A TEXTBOOK OF HISTOLOGY

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BY

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EIGHTH EDITION
REVISED

PREFACE

The general plan of the book remains unchanged. An effort has been made to incorporate the important additions to the subject of Histology as recorded in the recent literature, more especially in the *Anatomical Record* and the *American Journal of Anatomy*. There are many new illustrations from various sources duly credited. The chapter on the Blood has been entirely rewritten. The chapters on Muscle, the Endocrine Organs, the Female Reproductive System and the Blood Vascular System have been thoroughly revised. Other changes include removal of literature citations from the text, and elimination of the chapters on Histologic Technic and the Directions for Laboratory Work. Experience has shown that teachers of Histology prefer to prepare and use their own laboratory outlines, more suitable to variable local conditions. There is now so little time available in the general course in Histology for training in technical procedure, and there exist now so many special books on technical methods that a chapter on Technic no longer seems to serve any necessary purpose. The histological literature has had such a vigorous growth during the past decade that further text inclusion of references would seriously disrupt the thought continuity of the reader. Accordingly, all references are recorded as footnotes and reassembled in a bibliographical list at the end of the book. The aim was to make this list moderately extensive, to include all of the more important publications, for the convenience of the student who may wish to pursue the study of particular subjects beyond the restricted practical limits of the textbook. The author has tried to profit from thoughtful suggesions from many sources, and takes this opportunity to express his deep appreciation for much very generous cooperation.

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<div align="right">H. E. JORDAN</div>

demands, by putting the more essential and what we regard as additionally desirable in different type.

References to the recent literature are inserted for the student who may wish to consult the more important original works upon which the later developments of Histology have advanced.

We gratefully acknowledge our indebtedness for illustration and data taken from the recent and earlier literature, and our obligations to the publishers for their kindly help and courtesy.

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HARVEY ERNEST JORDAN ·
JEREMIAH S. FERGUSON

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CHAPTER I

THE PROTOPLASM AND THE CELL

Definition.—Histology is the science of tissue structure, plant or animal. It concerns itself, therefore, chiefly with the structural characteristics and interrelationships of the component elements of tissues. These elements are the *cells*, and the material connecting or separating the cells, the *intercellular substances*. A tissue consists of cells associated in the performance of a specific function. A cell may be defined in a preliminary way as the unit of organic structure and function. The minuter details of histology involve also cell anatomy or *cytology*. Here we meet with the essential substance of the cells, the *protoplasm*, or *bioplasm*, the "material basis of life." We also meet with the chief "organ" of cells, the *nucleus*. A more precise definition of a cell may accordingly be given as a *circumscribed mass of protoplasm containing a nucleus* (Fig. 1). A complete histologic description embraces, therefore, details of the relationships of the component cells of a tissue, and of the protoplasmic structure and nuclear characteristics of the types of cells involved. Histology includes further the data of tissue origin and development, or *histogenesis*, and of cell origin and development, or *cytogenesis*. Cells are the building stones of tissues; tissues combine to form organs; organs are associated into systems. Animal histology is accordingly a part of general anatomy; it is *tissue anatomy*, that part of human histology which considers the relationships between tissues in organs is sometimes spoken of as *microscopic anatomy*.

Fig. 1.—Various Spheroidal Cells.

1, ovum from ovary of a child; *2*, spermatocyte; and *3*, spermatid, from the testicle of a rabbit. Hematein and eosin. ×750

Historical Development.—Modern human histology had its origin in the work of Bichat (1771-1801). He did not employ the microscope; but his careful and extensive studies of the minute anatomy of tissues gave the impulse and general outline for later studies by means of the microscope through which mammalian histology has grown to a relatively complete science. Great impetus was given also by the announcement of the cell theory of Schleiden and Schwann in 1839, namely, the statement that all tissues are composed of structural units, or cells.
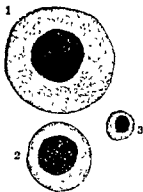
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It is an aggregate of *colloids* and *crystalloids*. The physicochemical laws which govern the crystalloids and colloids underlie the properties of living matter. An organism is essentially an aqueous solution, holding in suspension colloidal substances of great complexity. Crystalloids are divisible into two groups: electrolytes and nonelectrolytes. The one (salts, acids, bases) in solution conducts the electric current, the other (urea, sugar) does not. Colloids exist in two states, a liquid or *sol* state, and a *semisolid* or *gel* state. There exists no sharp line of division between colloids and crystalloids; these terms designate phases or states rather than substances; between them lie all kinds of intermediate grades. Protoplasm is a sol; and since its fluidity is due to water, it is commonly classed as a *hydrosol*. It passes
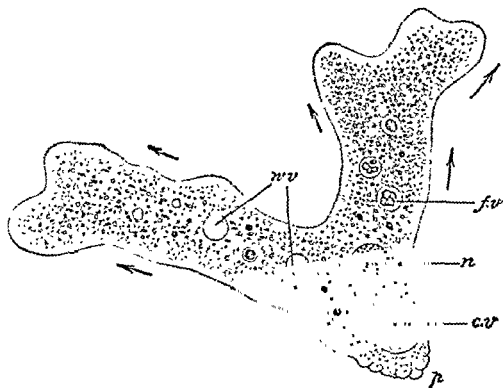

FIG. 2.—AMEBA PROTEUS IN MOTION.

c.v, contractile vacuole; *f.v*, food vacuole; *n*, nucleus; *w.v*, water vacuoles. The arrows indicate the direction of the protoplasmic flow. Note the peripheral nongranular ectoplasm, and the granular endoplasm. (From Calkins, *Biology*, H. Holt & Co., after Sedgwick and Wilson.)

readily into a gel condition, thus becoming a *hydrogel*. In living protoplasm this metamorphosis is a reversible process. Agents which effect an irreversible gelation of protoplasm tend to bring life to a standstill. Fixation, or killing, of tissue for microscopic study consists in a separation of the more solid part of colloidal protoplasm from a more liquid part. Death is histologically such a process of coagulation. Living protoplasm may be studied to good advantage in the one-cell animal forms, ameba (Fig. 2) or paramecium (Fig. 3). These and other equally favorable protozoan forms are readily available from hay infusion cultures, and can be profitably employed for the demonstration also of the simpler modes of proto-

In less complete form the cell theory had been advanced by earlier investigators, by Mirbel [1] (1808), by Lamark (1809) and by Dutrochet [2] (1824). Other epochal steps in histologic science were the recognition of the nucleus by Robert Brown in 1833, and of protoplasm by von Mohl in 1846. Cytology arose almost as an incident to embryology. It traces its origin to the work of O. Hertwig on the fertilization of the sea urchin's egg (1875) and the substantially identical observations, made independently and simultaneously by H. Fol. It is the infant anatomic science, its late development being due, largely, to its dependence upon the optical and mechanical refinements of the microscope. It deals with fundamental structures within the limits of visibility, and is destined to grow to vast proportions, as the already voluminous literature on mitochondria (plastosomes) in part foreshadows.

Relation to Other Biologic Sciences.—Histology aims to complete anatomic knowledge. It is thus the complement of gross anatomy. It furnishes also essential preliminary data for the understanding of pathology; abnormal structure and function become fully intelligible only in the light of normal histology. It is fundamental also to physiology, the science of normal function.

A certain function demands a specific structure; structure and function sustain reciprocal relationships. Normal function depends upon the normal structure of the cells involved in the function; abnormal function, or disease, is associated with altered cellular structure. Histology gains enormously in interest and value to the student who will keep in mind the function that a certain structure under consideration is called upon to perform. Embryology also to a considerable extent builds upon histologic and cytologic data.

PROTOPLASM

Chemical Constitution.—The unit of both structure and function is the cell. The essential constituent of cells is protoplasm. Protoplasm may be thought of as a physiochemical mechanism. Chemically, it is a very complex aqueous mixture of substances, containing the elements, carbon, oxygen, hydrogen, nitrogen, and small quantities of sulphur, phosphorus, calcium, sodium, chlorine, magnesium, potassium and iron.

The principal compounds of protoplasm are proteins, which furnish the main source of energy expended in function; carbohydrates; fats; water, which constitutes about three-quarters of its weight; and inorganic salts. It is believed by one school of biologists (mechanists) that if we had the formula for the proper stereo-isomeric association of the elements and compounds of protoplasm, life could be artificially produced; another school of biologists (vitalists) assume an additional vital principle as a prerequisite for life.

Physical Constitution.—Physically, protoplasm is a granular semifluid or gelatinous substance. It possesses properties characteristic of both solids and liquids.

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[1] Gerould, 1922.
[2] Goss, 1937.

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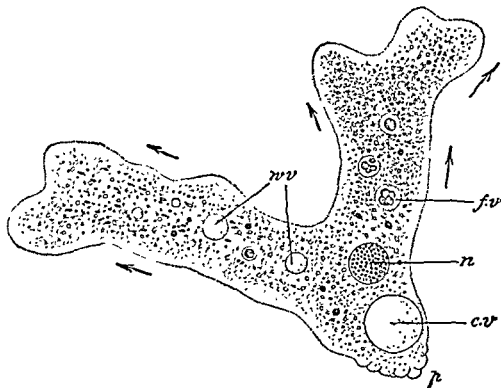and since its fluidity is due to water, it is commonly classed as a *hydrosol*. It passes

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plasmic activity, and of the changes suffered by protoplasm in passing
living to the dead condition. Since protoplasm is commonly organized
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THE CELL

A *generalized cell* is of spheroidal shape (unmodified by pressure)
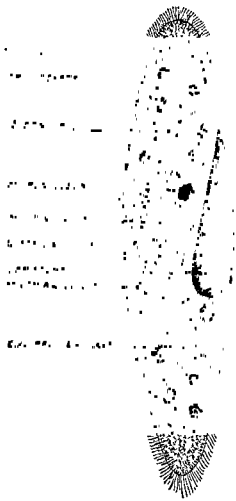tains certain organs and a variety of fundamental and secondary elements

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FIG. 3—PARAMECIUM CAUDATUM

Note the peripheral cilia and the
granulo-alveolar character of the proto-
plasm (From Calkins, *Biology,* H. Holt
& Co)

Nucleus.—The protoplasm composing the nucleus is known as *nucleoplasm*
karyoplasm; that constituting the remainder of the cell, the *cytoplasm.* The nuc
constituents include a more fluid ground substance or *nuclear sap* (*karyolym*

paralinin), throughout which extends a delicate reticulum of *linin* threads (Fig. 4). Upon these linin or achromatin threads are supported, more abundantly at the points of intersection of the mesh, granules (*chromioles*) and masses (*net knots*) of a substance staining deeply in the basic dyes, the *chromatin*. Spheroidal net knots are known as *karyosomes*. The linin is said to be achromatic. Whether it is chemically different from chromatin or simply more attenuated chromatin is disputed. The "chromatic" granules themselves undergo changes in stainability: on the basis of reaction to acid and basic dyes, this substance is divided into *oxy-*
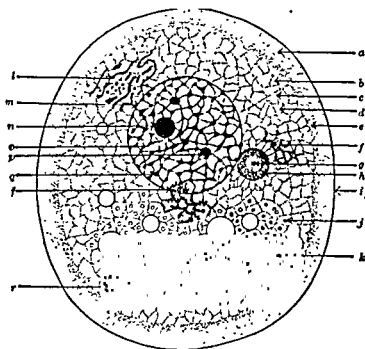

FIG. 4.—A GENERALIZED CELL.

a, exoplasm; *b*, endoplasm; *c*, spongioplasm; *d*, hyaloplasm; *e*, microsomes; *f*, chromidia; *g*, centrosome (centriole); *h*, centrosphere; *i*, cell membrane; *j*, deutoplasmic granule; *k*, fluid vacuole, or oil drop; *l*, mitochondria or plastosomes; *m*, nuclear membrane; *n*, nucleolus; *o*, linin; *p*, karyosome; *q*, chromatin (net knot); *r*, foreign inclusions, pigment, etc. (metaplasm).

chromatin (*lantanine*) and *basichromatin*. Linin and chromatin are regarded by some as different phases in the elaboration of the same substance. The nucleus includes, furthermore, usually one, frequently more, nucleoli. These do not grade into the nuclear sap, like the nuclear network, but are limited by a sharp line of demarcation. They may be achromatic, when they are known as *plasmosomes*, or they may take on chromatin, becoming *chromatin nucleoli*. It is uncertain whether the latter are identical in all cases with the karyosomes. The difference among nucleoli is more probably one of degree of abundance of chromatin. The nucleus is the metabolic organ of the cell; without a nucleus a cell may continue to live for a time, but it can neither grow nor undergo progressive differentiation. All changes in enucleated protoplasm are regressive, leading to death. The nucleus is also largely the reproductive center, as will be described below. The nucleolus

plasmic activity, and of the changes suffered by protoplasm in passing from the living to the dead condition. Since protoplasm is commonly organized into cells, the next step demands a knowledge of a typical or generalized cell.

THE CELL

A *generalized cell* is of spheroidal shape (unmodified by pressure) and contains certain organs and a variety of fundamental and secondary elements (Fig. 4).

A cell (or protoplast; Hanstein) is a mass of protoplasm endowed with vital properties. The confines of such a cellular mass of protoplasm exist in a *cell membrane*. This represents a differentiation product of protoplasm; when robust as in plant cells, it forms a *cell wall*. In certain cells, *e.g.*, white blood cells, it is apparently lacking; however, in these so-called naked cells the peripheral layer of protoplasm is more condensed and most probably subserves the osmotic function of a distinct membrane. In fact, the surfaces of protoplasm possess the properties of semipermeable membranes, probably lipoid in nature. An essential organ of the cell is the *nucleus*. It is trophic in function, the center of oxidation processes. In certain protozoa this is represented by scattered nuclear materials or granules (Fig. 5). The shape of the nucleus is spherical; typically it has a central location, but it frequently assumes eccentric positions. It is physically denser and more elastic than the extranuclear protoplasm. Its periphery simulates, or perhaps consists of, a membrane, the *nuclear wall*. Whether as a membrane it be complete or reticulated, whether of nuclear, cytoplasmic or composite origin, are undecided points. Certain results of investigations on the nuclear membrane suggest that it is fenestrated; such conditions would permit of an easy escape of nuclear material into the cytoplasm.

FIG. 3.—PARAMECIUM CAUDATUM.

Note the peripheral cilia and the granulo-alveolar character of the protoplasm (From Calkins, *Biology*, H. Holt & Co.)

Nucleus.—The protoplasm composing the nucleus is known as *nucleoplasm* or *karyoplasm*; that constituting the remainder of the cell, the *cytoplasm*. The nuclear constituents include a more fluid ground substance or *nuclear sap* (*karyolymph*;

material for certain differentiation products; *mitochondria-or blastosomes; trophospongium; Golgi apparatus*, and *tonofibrils.*
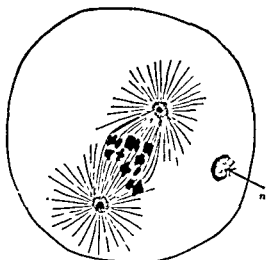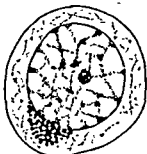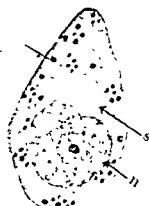

FIG 6. FIG 7. FIG 8.

FIG. 6—EGG OF A CLAM (CUMINGIA TELLINOIDES)

The first maturation spindle with centrosomes and chromosomes at metaphase, and the disappearing nucleolus (*n*) at the right ×1000

FIG. 7.—PRIMARY SPERMATOCYTE OF A TURTLE (CISTUDO CAROLINA).

Chromatic spherules (chromidia) apparently in process of extrusion from nucleus. ×1500.

FIG. 8.—SPERMATID OF OPOSSUM IN EARLY STAGE OF METAMORPHOSIS INTO A SPERMIUM.

Granular mitochondria; *m*, in the cytoplasm, *n*, nucleus; *s*, archoplasmic sphere. ×2000.

Mitochondria.—Mitochondria are cytoplasmic elements of very variable form and of almost universal distribution. These are destined to bulk very large in immediate cytological investigations. They may prove to be very important elements of the more fundamental protoplasmic structure and function. In the germ cells of vertebrates, as in undifferentiated cells generally, they are for the most part, granular (*chondriosomes*) (Fig. 8); in the somatic differentiated cells filamentous or rod-shaped (*chondriomites; chondrioconts; pseudochromosomes*) (Figs. 9, 10). Both chromidia and *trophospongium* (a canalicular network of the cytoplasm, probably concerned with circulation of nutritive material or secretion products) (Fig. 11) have been identified with mitochondria. Trophospongium at least is a distinct structure, and chromidia more probably also, though by some regarded as the elements from which the filamentous mitochondria are formed. Mitochondria have been credited with a great variety of functions, *e g.*, formation of presecretion and excretion granules, and the formation of various kinds of fibrils. M Heidenhain regards the chondriosomes as vegetative organs of the cells subserving metabolism. Our knowledge is as yet too limited to speak with assurance either as to their origin, complete function, or fate. One thing only is certain,

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Astral System.—Another organ of a typical cell is the aster, *astral system* or *ttraction sphere.* Its substance is collectively known as *archoplasm.* It usually lies butside of, but close to, the nucleus; in certain cells it is intranuclear, *e.g.,* sperma-

FIG. 5.—A UNICEL-
LULAR FLAGELLATE
ANIMAL (TETRA-
MITUS CHILOMO-
NAS)

The nuclear mate-
rial is distributed as
granules throughout
the cell (Redrawn
from Calkins)

tocytes of Ascaris. It consists centrally of a granule, the *centrosome* (cytocentrum); in this, in certain instances, may be differentiated centrally a smaller granule, the *centriole;* when the latter appears, the more outlying portion of the centrosome is designated the *centroplasm.* The centrosome may divide into two, becoming a *diplosome,* or in some instances it may become multiple, when it is known as a pluricorpuscular centrosome. Surrounding the centrosome is a clearer, minutely granular sphere, the *centrosphere;* radiating from this periph-erally are delicate astral rays, collectively known as the as-trosphere (Fig. 6). Structurally the aster is subject to con-siderable variations in different cells. On account of its rela-tion to cell division, it is regarded as the dynamic center of the cell; viewed thus its substance is known as *kinoplasm.* The attraction sphere may or may not be visibly present; in all living cells it, or its analogue, is generally believed to be po-tentially present.

Cytoplasm.—The cytoplasm or *cytosome* may be divided into a thin peripheral or cortical layer of less granular proto-plasm, the *exoplasm* (ectoplasm), and the main central mass, the *endoplasm.* In certain highly differentiated cells the exo-plasm is not discernible. In others, at certain stages in the development it contains the products of differentiation, when it is known as "deuteroplasm" (Studnicka). The endoplasm is commonly described as consisting of a more fluid, finely granular ground substance, the *hyaloplasm (paraplasm, inter-filar mass, paramitome, enchylema, cytolymph),* containing a delicate denser reticulum, or *cytoreticulum,* with polygonal or spheroidal meshes. The substance of the reticulum is called *spongioplasm (mitome; filar mass).* It is held by some to be continuous with the linin mesh of the nucleus The granules of the ground substance, both free of and attached to the spongioplasm, are called *microsomes.* According to one interpretation the spongioplasm arises by coalescence of microsomes. A more recent interpretation regards both network and granule as simply more condensed portions of the hyaloplasm. The cytoplasm may contain, besides the aforementioned fundamental constituents, nutritive materials including yolk granules or globules *(deutoplasm)*, vacuoles, foreign inclosures, *e.g ,* bacteria, etc., and pigment *(metaplasm)*; *plastids* (in plant cells); *chromidia* (Fig. 7), masses of chromatic granules, presumably of nuclear origin, and probably the raw

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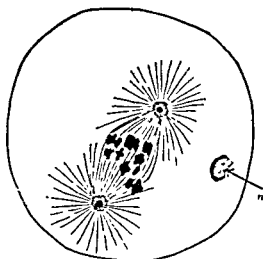

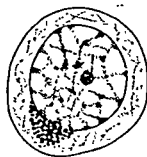FIG 6.   FIG 7.   FIG 8.

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Fig 5.—A Unicellular Flagellate Animal (Tetramitus Chilomonas).

The nuclear material is distributed as granules throughout the cell (Redrawn from Calkins)

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material for certain differentiation products; *my*
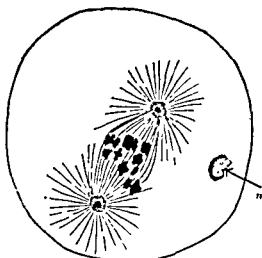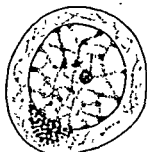*spongium*; *Golgi apparatus*, and *tonofibrils*
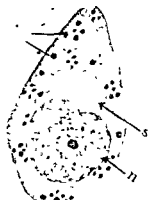

FIG. 6.   FIG 7.   FIG 8.

FIG 6—EGG OF A CLAM (CUMINGIA TELLINOIDES)

The first maturation spindle with centrosomes and chromosomes at metaphase, and the disappearing nucleolus (*n*) at the right ×1000

FIG. 7—PRIMARY SPERMATOCYTE OF A TURTLE (CISTUDO CAROLINA).

Chromatic spherules (chromidia) apparently in process of extrusion from nucleus ×1500

FIG. 8.—SPERMATID OF OPOSSUM IN EARLY STAGE OF METAMORPHOSIS INTO A SPERMIUM. Granular mitochondria; *m*, in the cytoplasm; *n*, nucleus; *s*, archoplasmic sphere. ×2000

Mitochondria.—Mitochondria are cytoplasmic elements of very variable form and of almost universal distribution. These are destined to bulk very large in immediate cytological investigations. They may prove to be very important elements of the more fundamental protoplasmic structure and function In the germ cells of vertebrates, as in undifferentiated cells generally, they are for the most part, granular (*chondriosomes*) (Fig. 8); in the somatic differentiated cells filamentous or rod-shaped (*chondriomites; chondrioconts; pseudochromosomes*) (Figs. 9, 10). Both chromidia and *trophospongium* (a canalicular network of the cytoplasm, probably concerned with circulation of nutritive material or secretion products) (Fig 11) have been identified with mitochondria. Trophospongium at least is a distinct structure, and chromidia more probably also, though by some regarded as the elements from which the filamentous mitochondria are formed. Mitochondria have been credited with a great variety of functions, *e.g.*, formation of presecretion and excretion granules, and the formation of various kinds of fibrils. M Heidenhain regards the chondriosomes as vegetative organs of the cells subserving metabolism Our knowledge is as yet too limited to speak with assurance either as to their origin, complete function, or fate. One thing only is certain,

namely, that they are actual constituents of the cytoplasm of practically every type of cells, at certain, perhaps all, stages of development and active function. They
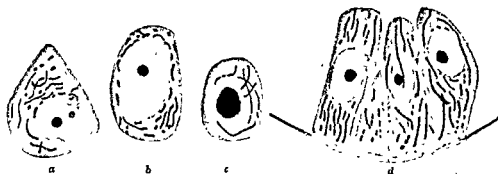

FIG. 9—CELLS FROM THE NEWLY HATCHED RAINBOW TROUT, TREATED ACCORDING TO MEVES'
TECHNIC FOR THE DEMONSTRATION OF MITOCHONDRIA (PLASTOSOMES).

a and *b*, cartilage cells; *c*, young blood cell; *d*, epithelial cells from the intestine. ×2000.
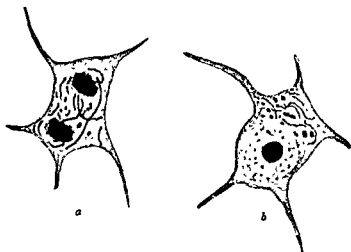

FIG. 10—TWO CELLS FROM THE MESENCHYMA OF THE NEWLY HATCHED RAINBOW TROUT.

The one to the left (*a*) at late anaphase of mitosis, showing mitochondria (plastosomes). Meves' technic. ×2000.

have been seen and studied in living plant cells,[3] and in animal cells grown in artificial media they have been observed[4] to move, to change shape, to divide into granules and again to reunite into filaments—facts which render inadmissible their interpretation in fixed material as lipoid precipitation products (Faure-Fremiét), and strongly suggest their connection with metabolic activity. They have the chemi-

3 Maximow, 1908.
4 Lewis, W. H., and Lewis, M. R, 1915

cal composition of a lipoid (probably a phosphatide) united to an albuminoid base. It has been suggested that they are a support to, and the region of, oxidation. Certain investigators (Benda, Meves, Duesberg) regard them as the cyto- plasmic basis of heredity, and ascribe to them an important rôle in histogenesis. Wallin[5] regards them as symbiotic bacteria. It is very probable that rods and granules in certain protozoa described as mitochondria were actually bacteria. (E. De Witt Miller, *J. Morph.*, 1937.)

The *internal reticular apparatus of Golgi*, in "fixed" material, occurs typically in the form of a network (Golgi net) closely adja- cent to or encircling the nucleus (Fig. 12). In the living cell stained with methylene blue the "Golgi apparatus" appears generally in the form of "a series of chromophilic vesicles each of which may en- circle a colorless chromophobe". (Whorley, L C., *J Morph.*, 1944) The chromophobic portion is regarded as the "developing product". These Golgi vesicles (bodies), following fixation with osmic acid, may become modified through collapse and fusion into a reticular structure. Like mitochondria, Golgi bodies readily reduce osmic acid and assume a dark brown color The Golgi apparatus is generally believed to be associated with the metabolic activity of the cell, especially with the secretory process and with the elaboration of fats and proteins. Claims have been advanced that the trophospongium of Holmgren (canalicular apparatus, Fig. 11) represents the negative image, in the form of empty canals, of the Golgi apparatus. The Golgi vesicles have also been identified with the "vacuome" of Parat, and the Golgi bodies (granules) with mito- chondria. Most of the recent evidence favors the conclusion of morphologic and genetic independence among Golgi apparatus, trophospongium, mitochondria and chromidia.

FIG. 11.—INTRACEL- LULAR NETWORK, OR TROPHOSPON- GIUM, WITHIN A PURKINJE CELL OF THE CEREBEL- LUM OF STRIX FLAMMEA.

Golgi's stain. (Golgi.)

Tonofibrils.—The term tonofibrils ("inofibrils," Tello, Cajal) was introduced by M. Heidenhain to designate certain "supporting fibrils" in epithelial cells, very strikingly
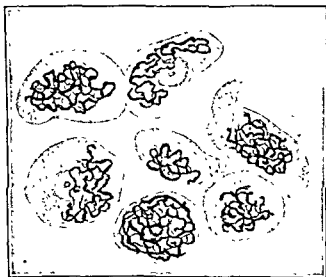

FIG. 12—DECIDUAL CELLS OF HUMAN PLACENTA AT TERM.

Note the internal reticular apparatus of Golgi. (Vecchi.)

represented in the relatively wide and coarse intercellular bridges and their intracellular approaches in the prickle cell layer of the stratified squamous epithelium of human skin

[5] Wallin, 1927, [6] Beams, 1931

FIG. 13.—TONOFIBRILS
IN EPITHELIAL CELL
OF INTESTINE OF
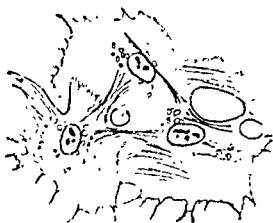FROG ×2300

(Redrawn from M. Heidenhain)

FIG. 14.—TONOFIBRILS IN EPITHELIAL CELLS
OF 48-HOUR GROWTH FROM AMNION OF
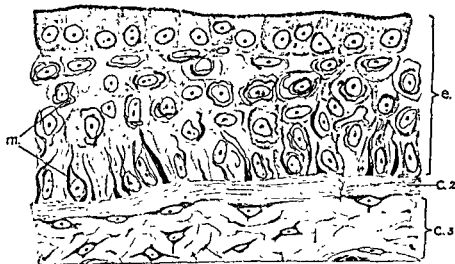5-DAY CHICK EMBRYO.

Mallory's stain. (Redrawn from M. Lewis.)

FIG. 15.—VERTICAL SECTION OF SKIN OF HIND LIMB OF FROG TADPOLE, SHOWING TYPICAL
TONOFIBRILS IN THE BASAL LAYER. ×600 (Speidel.)

(Fig. 38). Such fibrils are widely present in epithelial cells under conditions requiring a certain degree of protoplasmic rigidity to prevent excessive deformation against factors of strain and pressure. They are most prominently disclosed with the iron hematoxylin staining technic. Good examples of tono-fibrils are shown in the columnar cells lining the intestine of the frog (Fig. 13) and the squamous cells of the amnion of the chick (Fig. 14). They appear conspicuously also in the columnar cells of the basal layer of the epidermis in human skin (Fig. 276) where they simulate a striated or denticulated border. These coarse perpendicular basal fibers are apparently identical with those of the skin of certain frog tadpoles (Fig. 15), originally described by Eberth (1866) and since then variously interpreted as supporting elements,[7] mitochondria[8] and connective tissue processes.[9]

The concept of tonofibrils has been erroneously extended to include also the initial fibrils of fibroblasts,[10] in their coarser form identical with the fibroglia fibers of Mallory,[11] the primitive fibrils of leiomyoblasts and those of spongioblasts. These specific original fibrils of connective tissue cells, smooth muscle cells and neuroglia stain equally well with iron hematoxylin, but can be readily discriminated from true tonofibrils on the basis of a differential staining reaction in special technics and on the basis of their genetic relation to definitive reticulum fibrils, myofibrils and glia fibers, respectively. The very similar fibers ("rootlets") of certain ciliated cells (Fig. 16) are apparently analogous with tonofibrils, but have in addition to their function of providing rigidity to the cell as a whole also that of serving as a support for the lashing cilia. Furthermore, their mode of origin is very different from that of tonofibrils, they arise as intracellular sprouts from the basal bodies to which the cilia are attached. Columnar cells with nonmotile cilia, as in the case of the epididymis, are provided with tonofibrils identical with those of nonciliated cells. Bensley[12] makes the interesting suggestion that tonofibrils are irreversible products of a fundamental fibrous constituent of protoplasm which he designates "plasmosin."

FIG 16—THREE CILIATED CELLS FROM THE BILE DUCT OF THE SNAIL, HELIX HORTENSIS.

The cells have a single row of basal granules, to which both cilia and rootlets are attached. ×2300. (M. Heidenhain.)

[7] Studnicka, 1908.
[8] Saguchi, 1913.
[9] Weed, 1934.
[10] Maximow, 1929.
[11] Mallory, 1904
[12] Bensley, R. R., 1938.

PROTOPLASMIC STRUCTURE OF CELLS

Four main types of protoplasmic structure are generally recognized: (1) the homogeneous; (2) the granular; (3) the alveolar or foam type; and (4) the fibrillar (Fig. 17). Varieties of fibrillar protoplasm occur as the reticular or sponge type and the filar type. The type of protoplasm of a particular cell may vary with the stage of development and function. In successive stages of development and differentiation the protoplasm of the same cell may pass from the apparently homogeneous, through the granular and granulo-alveolar, to a granulofibrillar type. Homogeneous protoplasm, as for example the ectoplasmic layer of ameba, is more probably to be interpreted as composed of minute, perhaps ultramicroscopic, colloidal granules (colloidal biogens). Young and undifferentiated cells commonly have a granular cytoplasm. In general it may be said tha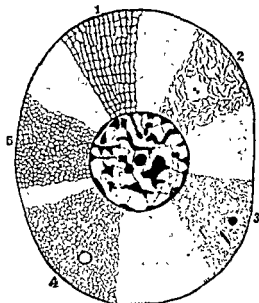t the actual fundamental type of protoplasm is the granular. This changes into the alveolar type by the appearance of spherules among the granules. The contents of the alveoli constitute the alveolar substance; the interalveolar sap, the hyaloplasm; the granules, the microsomes; and the walls of the alveoli may be identified with the spongioplasm of the reticular type of protoplasm. Another interpretation of alveolar protoplasm regards the content of the alveoli as hyaloplasm. The microsomes may in part be closely associated with the alveolar walls, perhaps forming them and the spongioplasm by the process of coalescence. The so-called alveolar protoplasm is in reality of the granulo-alveolar type. The spherules probably arise, at least in part, by a process of liquefaction of some of the granules The alveologranular is probably the commonest type of protoplasm. The process of transformation of the granular into the alveolar type can best be demonstrated in young growing eggs of invertebrates. Figure 18 shows an egg in which the perinuclear protoplasm is predominantly

FIG. 17.—THEORIES OF PROTOPLASMIC STRUCTURE.

1, alveolar structure; granules occur only at the angles formed by the alveoli *2,* filar structure, showing filar and interfilar substance The centrosome (a diplosome) is represented in this portion; it is surrounded by a clear attraction sphere *3,* granular structure; coarse microsomes irregularly disposed. This portion contains three foreign bodies which have been included by the cell, a streptococcus, a crystal and a spheroidal pigment mass. *4,* the alveolar walls are formed by regularly arranged microsomes; a vacuole is shown in this section *5,* reticular structure The cell is inclosed by a cell membrane, and contains a central nucleus in which are shown the nuclear membrane, indistinct linin fibrils, deeply stained chromatin in coarse threads and irregular masses (karyosomes), and a centrally situated nucleolus or plasmosome.

alveolar, the more peripheral portion granular. The metamorphosis is apparently under the control of the nucleus.

Other commonly described types of protoplasmic structure may be interpreted in terms of mechanical (extraneous; artificial) alterations in the alveolar type.
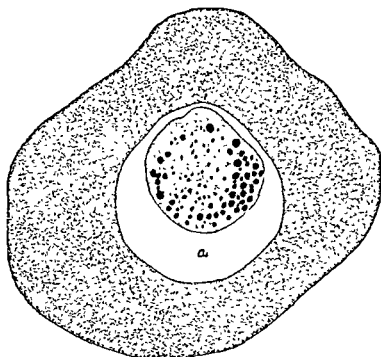

FIG. 18.—EGG OF THE BLOOD STARFISH (CRIBRELLA SANGUINEOLENTA) IN LATER GROWTH PERIOD

A stage in the change of an earlier granular to a later alveolar condition of the cytoplasm. The nucleus contains many spherical nucleoli of various sizes. The space (*a*) is a fixation artifact ×1500.

Thus a *reticular* type may be derived from the alveolar through modification (by pressure, or distortion) of the spherical alveoli into polyhedral or irregular compartments. Likewise the *fibrillar* or *filar* types may be interpreted as similar more extensive modifications resulting in ruptures of the alveoli and consequent finer or coarser indiscriminate aggregations of spongioplasmic fibrils, or as the result of the coalescence of granules to form fibrils. The distinction between fundamentally granular and alveolar protoplasm, and secondarily derived types of granular and reticular (fibrillar) protoplasm must be emphasized. In the performance of specific functions, certain cells elaborate secretory granules (gland cells, Figure 19; nerve cells, Figure 20; cells with crystalloids, Figure 21); others produce various types of fibrils (*e.g.*, nerve cell, Figure 22; connective tissue cells, and muscle cells); others elaborate fat spherules (*e g.*, Figure 23); and still others a canalicular (trophospongium) apparatus (Fig. 24).
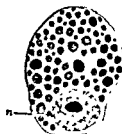

FIG. 19.—PANCREAS CELL OF TURTLE, FILLED WITH ZYMOGENIC GRANULES

n, nucleus, with nucleolus. ×2000.

The foregoing description of protoplasmic structure pertains largely to the "fixed" (dead) condition. In this connection the terminology employed will continue useful. But the more refined physicochemical studies of *living* protoplasm

FIG. 20.—MOTOR NERVE CELL FROM THE VENTRAL HORN OF THE SPINAL CORD OF THE OX.

Nissl granules in the cell body and its dendritic processes. The nongranular process at the left is the axon *p*, pigment. (From Barker, *The Nervous System*, after von Lenhossék.)

FIG. 21.—INTERSTITIAL CELL FROM THE TESTIS OF A TWENTY-ONE-YEAR-OLD MAN, SHOWING GRANULAR AND FILAMENTOUS MITOCHONDRIA.

(Winiwarter)

FIG. 22.—A NEURON (GIANT PYRAMIDAL CELL, OR CELL OF BETZ) FROM THE CEREBRAL CORTEX OF MAN, SHOWING THE NEUROFIBRILS.

Bielschowsky technic. ×500

have aroused considerable skepticism respecting the verity of actual specific structures corresponding to the designations applied, more especially the spongioplasmic and linin network. Perhaps the most that can be said with certainty regarding

the fundamental structure of protoplasm is to describe it as a granular gel. Kite's [13] studies of the physical properties and molar structure of protoplasm in various cells, by combined methods of microdissection and vital staining, have led to clearer conceptions in this field. He interprets protoplasm as an *emulsoid*, the real structural units of which are the colloidal particles, and conceives of the optical image as the result of the combination of the physical phenomena of reflection, refraction, diffraction, absorption, dispersion, interference, and a scattering action on light. Living protoplasm is an apparently homogeneous and viscous hydrogel, holding in suspension in the form of granules (microsomes) minute masses of denser

FIG. 23.—DEVELOPING FAT CELLS

The fat droplets, after extraction with alcohol and ether, appearing as vacuoles. Hematein and eosin ×550.

FIG 24.—COLUMNAR EPITHELIAL CELLS OF THE EPIDIDYMIS SHOWING CANALICULAR APPARATUS

(Holmgren.)

gels, and liquid globules (alveoli) which show many of the optical properties of an oil drop. The network and granules of the nucleus he regards as optical phenomena, areas of greater concentration in the nuclear gel, not separated from, but grading into the surrounding diluter gel of the nuclear sap. Spindle fibers were successfully dissected out of the protoplasm as distinct, relatively rigid threads. These conclusions are in the main in accord with those deduced from the earlier physicochemical studies of protoplasm and colloids by Hardy and others. M. R. and W. H. Lewis [14] also find no sign of a reticular or of an alveolar structure in either cytoplasm or nucleus in cells studied in tissue cultures. They describe both cytoplasm and nucleus as "finely granular, almost homogeneous in appearance."

VITAL PROPERTIES OF CELLS

Living protoplasm is capable of certain specific reactions (physiological processes) or functions. These reactions are spoken of as vital properties or attributes of protoplasm. They are general properties of living matter. They include primarily: metabolism, irritability, contractility and reproduction.

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[13] Kite, 1913.
[14] Lewis, W H and Lewis, M. R., 1915

The foregoing description of protoplasmic structure pertains largely to the "fixed" (dead) condition. In this connection the terminology employed will continue useful. But the more refined physicochemical studies of *living* protoplasm
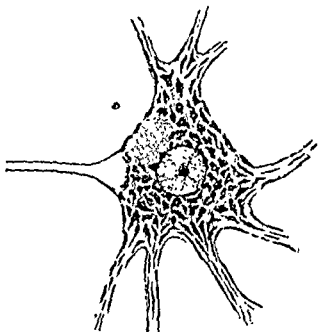

FIG. 20.—MOTOR NERVE CELL FROM THE VENTRAL HORN OF THE SPINAL CORD OF THE OX.

Nissl granules in the cell body and its dendritic processes. The nongranular process at the left is the axon. *p*, pigment (From Barker, *The Nervous System*, after von Lenhossék.)
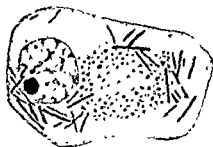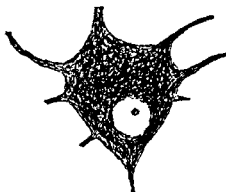

FIG. 21.—INTERSTITIAL CELL FROM THE TESTIS OF A TWENTY-ONE-YEAR-OLD MAN, SHOWING GRANULAR AND FILAMENTOUS MITOCHONDRIA.

(Winiwarter.)

FIG. 22.—A NEURON (GIANT PYRAMIDAL CELL, OR CELL OF BETZ) FROM THE CEREBRAL CORTEX OF MAN, SHOWING THE NEUROFIBRILS.

Bielschowsky technic. ×500

have aroused considerable skepticism respecting the verity of actual specific structures corresponding to the designations applied, more especially the spongioplasmic and linin network. Perhaps the most that can be said with certainty regarding

ameba; hence the name. This consists essentially in the formation of a proto-plasmic process or *pseudopodium*, into which the main mass of protoplasm flows, thus producing progression (Fig. 25). The movement of the white blood corpuscles is of this sort (Fig. 26).

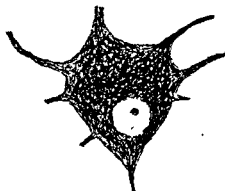*Ciliary Motility.*—Ciliary motil-ity is characteristic of hair-like processes of certain cells; such proc-esses or *cilia* represent essentially permanently differentiated delicate pseudopodia. The method of cilium formation is illustrated in its sim-plest form in the transient vibratory processes that arise under certain conditions on leukocytes (Fig. 237).

FIG. 26—A LEUKOCYTE FROM HUMAN BLOOD IN ACTIVE AMEBOID MOTION.

The figures indicate the successive forms as-sumed by the cell. Drawings were made at inter-vals of one minute. ×500.

In metazoa generally ciliated cells are attached, motion being limited to the cilia, which are located on the free border. The function of cilia is to propel secretions toward the surface. The motion is wave-like and always in one direction. The cilia are generally attached to a double row of granules, the "basal bodies" (Fig. 27), perhaps partition products of the centrosome. In protozoa, *e.g.*, Paramecium (Fig. 3), the entire surface of the cell may be ciliated; the function of the cilia here being progression, and the direction of stroke is reversible. Certain cilia are nonmotile, *e.g.*, in the epididymis, where they are closely clumped into brush-like masses (Fig. 30). The function of such cilia is, in part at least, to furnish a means for the elimination of secretions. *Flagellate motion* is to be regarded as a variety of ciliary motion. A *flagellum* is commonly regarded as a more robust cilium. The purpose of flagella is to propel the higher cells to which they are attached. Usually in higher animals the number of flagella is limited to one to a cell. The best examples of flagella are furnished by spermatozoa (Fig. 28).

FIG. 27—THREE CELLS FROM A DUCTULUS EFFERENS OF THE TESTIS OF THE RABBIT.

The nonciliated cell has a dip-losome at its free border. The adjacent ciliated cells have in place a double row of basal gran-ules to which the motile cilia are attached. (von Lenhossék.)

Molecular Motility.—Molecular motility is a dancing or oscillatory movement of the granules in living protoplasm. Such granules may be non-living matter, pigment, etc. This type of motion is also called *brownian movement*. It is probably purely a physical phenomenon. It may be simu-lated by mixing finely divided carmine with glycerin.

Circulatory Motility.—Circulatory or streaming movement occurs in various degrees in probably all living protoplasm. It is only when it is rapid that it be-comes easily discernible. It is readily demonstrable in certain plant cells, *e.g.*, chara, nitella and elodea; also less readily in certain protozoa (Paramecium). It must

Metabolism.—Metabolism is that property of living protoplasm by virtue of which it can elaborate from raw food material the complex chemical compounds of protoplasm (anabolic phase, constructive metabolism, assimilation), and convert the same into kinetic energy for the performance of specific *functions* (katabolic phase, destructive metabolism, dissimilation), *e.g.*, secretion and excretion. Metabolism generally involves growth and *differentiation*. Development also is fundamentally a metabolic process, and in essence consists of "a progressive differentiation of complex and specialized structures and functions from relatively simple and generalized beginnings" (Conklin).

Irritability.—Irritability or sensitivity, is a fundamental or general property of protoplasm. It is characterized by a capacity to receive and make response to stimuli, by changes of vital processes. Its prerequisite is the protoplasmic property of *conductivity*, and its expression in many instances depends upon the property of *contractility*. In a comprehensive sense, stimulus is every alteration in the external
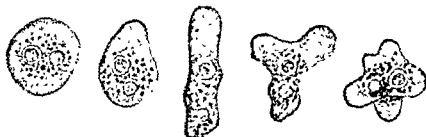

FIG. 25.—SUCCESSIVE STAGES IN THE MOVEMENT OF AN AMEBA.
The cells contain a nucleus, a contractile vacuole and protoplasmic granules. (Verworn.)

vital condition (Verworn). The reaction to stimuli may exhibit itself in one of three modes: functional, nutritive, and formative (Verworn). Stimuli are of various sorts, *e.g.*, thermal, mechanical, chemical, photic, solar, galvanic (electric), fluid, current, gravity. The simplest resulting reactions, expressed in unicellular forms in terms of orientation (tropism) or contact (taxis)—represented by automatic responses or reflexes in higher forms—are respectively thermotropism, stereotropism (barotaxis; thigmotaxis), chemotropism, phototropism, heliotropism, galvanotropism, hydrotropism, rheotropism, and geotropism. Response may be *either toward or away from a source of stimulus*. In the case of the electric current or water currents, for example, simple organisms may orient themselves, or protoplasm may move, in line with or opposite to the current; these opposite reactions are called positive and negative *tropisms* respectively. Responses involve fundamentally metabolic changes.

Contractility.—Motion results from response to certain stimuli, that is, by reason of irritability; and it is dependent upon the vital phenomenon of *contractility*. Motion is of various types, predominant among which are (*a*) ameboid, (*b*) ciliary, (*c*) molecular, (*d*) circulatory (streaming; protoplasmic) and (*e*) muscular.

Ameboid Motility.—Ameboid motility is exemplified in the movements of an

or "cytoblastema," the inorganic may continually be passing into the primary organic, *e.g.*, monera (Haeckel), but not perceptible under our present means of search and observation.

However, in histology we need to be concerned only with the derivation of cells from preëxisting cells This proceeds in one of two ways: (*a*) direct, amitotic, or akaryokinetic; and (*b*) indirect, mitotic, or karyokinetic. The difference between the two inheres in a difference in behavior on the part of the nucleus (or karyon). Comparative studies of the lower groups of animals and plants have revealed a fairly complete series of intermediate stages. On the basis of these facts it is believed by some that amitosis is the primitive method of cell multiplication, mitosis the derived or more highly specialized type. Others regard amitosis as the derived, not the primitive form of division.

Cell division is presumably due to the fact that the area of the surface increases as the square, the volume as the cube, of the diameter. In consequence, the surface
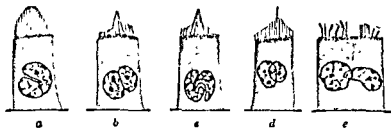

FIG. 30—SUCCESSIVE STAGES IN THE AMITOTIC DIVISION OF THE CILIATED CELLS LINING THE DUCTUS EPIDIDYMIDIS OF THE MOUSE. ×1500.

of a growing cell becomes increasingly restricted relative to its bulk, accordingly increasingly less efficient as a mechanism for the intake of adequate nutritive materials. The time then arrives when the center must suffer nutritive want or when the nucleus becomes unable to exert its trophic functions at the distance of the advancing periphery Division of such an enlarged cell into two smaller cells reëstablishes the original and more favorable nucleo-cytoplasmic dimensional relationship.

Amitosis.—In typical amitosis the nucleolus first becomes bilobed and then divides (Fig. 29). This is followed by nuclear division, each resulting nucleus inclosing one of the nucleoli. Nuclear division is followed by cytoplasmic division. A centrosome is generally neither active nor even visible during this process. This typical condition is rarely realized. It was first described by Remak (1841) for blood cells. Usually nuclear division is independent of nucleolar fission, which may be lacking (Fig 30). The nuclear fission proceeds variously by a medial or submedial annular constriction, or by progressive linear indentation of some portion of the surface. In certain instances the division takes place inside of the original nuclear membrane. The nuclear products may be of unequal size, and multiple (Fig. 31). Generally cytoplasmic division lags far behind nuclear division, or may even fail to appear, thus producing bi- or multinucleate cells. Amitosis effects a mass division of the nucleus; neither spirem nor chromosomes nor

most probably be interpreted as a form of respiration. It is characterized by a flowing or streaming of the protoplasmic granules in a definite direction.

Muscular Motility.—The reason for listing *muscular* as a separate type of motility is mainly its predominance in animals and the fact that it does not apparently fully conform to any of the above types. It is characterized by a reversible

process of contraction of specially differentiated muscle fibrils. It perhaps most closely resembles streaming motility. It leads to least confusion, in view of our present lack of definite knowledge regarding the physical and chemical phenomena underlying muscular motion, to speak of it as a distinct type. It will be further discussed under Muscle.
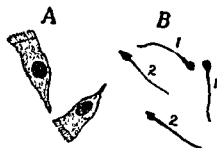
FIG. 28.—CILIATE AND FLAGELLATE CELLS.

A, ciliated cells isolated from the trachea of a cat. *B,* human spermatozoa, *1,* in surface view; *2,* in profile. Examined fresh in normal saline solution. ×550.

Reproduction.—The essence of reproduction is cell multiplication. A living cell has the power of producing other cells like itself. Viewed philosophically, cells may conceivably arise in two different ways: (1) from nonliving material, spontaneous generation (abiogenesis); (2) from preëxisting cells by division. Science has quite generally accepted the aphorism, *omnis cellula e cellula* (Virchow) as an expression of the whole truth. However, full acceptance of the doctrine of evolution logically

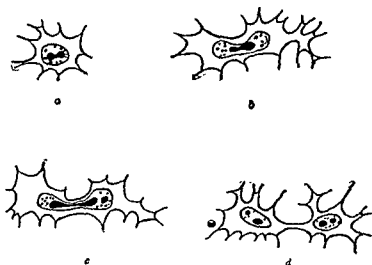FIG. 29.—SUCCESSIVE STEPS IN AMITOTIC DIVISION IN TENDON CELL OF NEWBORN MOUSE. ×800 (Nowikoff.)

compels belief in spontaneous generation: this not in any such crude form as that frogs may arise from the mud of rivers, or insects from dew or dung, but that given the conditions (conceivably possible somewhere in the universe today) prevalent when life first appeared as the original mass of living protoplasm, the "cytode,"

or "cytoblastema," the inorganic may continually be passing into the primary organic, *e g.*, monera (Haeckel), but not perceptible under our present means of search and observation.

However, in histology we need to be concerned only with the derivation of cells from preëxisting cells. This proceeds in one of two ways: (*a*) direct, amitotic, or akaryokinetic; and (*b*) indirect, mitotic, or karyokinetic. The difference between the two inheres in a difference in behavior on the part of the nucleus (or karyon). Comparative studies of the lower groups of animals and plants have revealed a fairly complete series of intermediate stages On the basis of these facts it is believed by some that amitosis is the primitive method of cell multiplication, mitosis the derived or more highly specialized type. Others regard amitosis as the derived, not the primitive form of division.

Cell division is presumably due to the fact that the area of the surface increases as the square, the volume as the cube, of the diameter. In consequence, the surface

FIG. 30—SUCCESSIVE STAGES IN THE AMITOTIC DIVISION OF THE CILIATED CELLS LINING THE DUCTUS EPIDIDYMIDIS OF THE MOUSE. ×1500.

of a growing cell becomes increasingly restricted relative to its bulk, accordingly increasingly less efficient as a mechanism for the intake of adequate nutritive materials. The time then arrives when the center must suffer nutritive want or when the nucleus becomes unable to exert its trophic functions at the distance of the advancing periphery. Division of such an enlarged cell into two smaller cells reëstablishes the original and more favorable nucleo-cytoplasmic dimensional relationship.

Amitosis.—In typical amitosis the nucleolus first becomes bilobed and then divides (Fig. 29). This is followed by nuclear division, each resulting nucleus inclosing one of the nucleoli. Nuclear division is followed by cytoplasmic division. A centrosome is generally neither active nor even visible during this process. This typical condition is rarely realized. It was first described by Remak (1841) for blood cells. Usually nuclear division is independent of nucleolar fission, which may be lacking (Fig. 30). The nuclear fission proceeds variously by a medial or submedial annular constriction, or by progressive linear indentation of some portion of the surface. In certain instances the division takes place inside of the original nuclear membrane. The nuclear products may be of unequal size, and multiple (Fig. 31). Generally cytoplasmic division lags far behind nuclear division, or may even fail to appear, thus producing bi- or multinucleate cells. Amitosis effects a mass division of the nucleus; neither spirem nor chromosomes nor

achromatic spindle, so conspicuous in mitosis, appear. Until recently amitosis was generally regarded as a relatively rare and unimportant process. It was supposed to be associated only with highly specialized and pathological conditions leading inevitably to death. Cells once having suffered amitotic division were believed not to be capable thereafter of dividing mitotically. The work of Child [15] reveals, however, that it is probably of wide occurrence. Instances have been described in most of the animal groups, including the vertebrates. He has shown its occurrence in regions of rapid growth, as in various embryonic tissues, *e.g.*, blastoderm of chick, and where a secretion is elaborated or in places of reserve formation. These facts may be harmonized with its occurrence in starving, degenerating tissues on
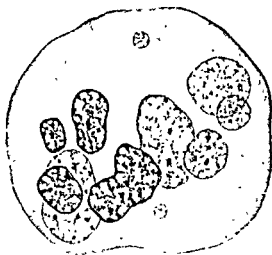

FIG. 31. — MULTINUCLEATED GIANT CELL, FROM THE YOLK SAC OF A 10 MILLIMETER PIG EMBRYO. ×2000.
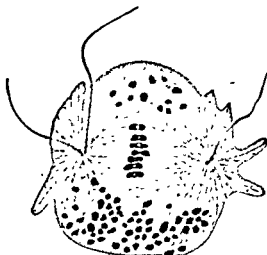
FIG. 32. — SPERMATOCYTE OF PYERIS CRATEGI, A BUTTERFLY, SHOWING A CILIUM ATTACHED TO THE CENTROSOME.

(Meves.)

the basis of a common underlying condition, namely, relative scarcity of nutritive material. Wieman [16] conceives of amitosis as due to scarcity of oxygen supply.

Where mitosis and amitosis are simultaneously present, it is more frequently the cells with the large nuclei, surrounded by a considerable amount of undifferentiated cytoplasm, that divide by mitosis. The factors underlying amitosis most probably exert their final effect indirectly through initial influence upon the centrosome. The best experimental evidence in favor of this view is supplied by Nathansohn who grew Spirogyra, normally dividing by mitosis, in a 1 per cent solution of ether in water, when the cells divided amitotically. On transference to pure water, the cells again divided mitotically. The ether seems to have exerted an inhibitory effect upon the kinoplasm (centrosome material), compelling division by amitosis. Amitosis is now generally conceded to be of wide occurrence under

15 Child, 1907.
16 Wieman, 1910.

certain conditions and in certain cells, but it is still quite unanimously disbelieved to occur in germ cells. In the latter it has perhaps not yet been certainly demonstrated to occur in cells actually in the germ cycle. In Mammalia amitosis can be demonstrated in the intermediate layers of stratified squamous (skin), transitional (bladder) and certain ciliated (epididymis, Fig. 30) epithelia; in the medulla of the adrenal, and in decidual cells. In ciliated epithelia this mode of division is perhaps associated with a partition of the centrosome in the formation of cilia. This will be further discussed in Chapter II under Ciliated Epithelium. This view is supported by the fact that the flagella of spermatozoa arise from the centrosome, and the observation that in certain cells the centrosome of mitotic spindles develops cilia (Fig. 32).

Mitosis.—This is the prevailing type of cell division. It was first described in complete outline by W. Flemming in 1878. For convenience of description the process, which must of course be thought of as continuous, may be divided into *prophase, metaphase, anaphase,* and *telophase.* An alternative and preferable terminology employs the words anaphase (prophase), mesophase (metaphase) and kataphase (anaphase and telophase). These phases involve coincident changes in the nucleus and the archoplasm (attraction sphere, Fig. 33, *A* to *J*) Mitotic figures can be seen in all rapidly growing tissues. The process is an essentially similar one throughout the plant and animal kingdoms; variations relate only to details associated chiefly with the archoplasm. The most favorable locations for study of mitosis are the growing tips of roots of certain plants, *e.g.,* onion, hyacinth, dogtooth violet; amphibian tissue (particularly skin and blood cells), and the testes of grasshoppers. Mitosis in germ cells involves certain specialized features, and calls for additional theoretical consideration; hence the description of these *maturation mitoses (meiosis)* will be reserved for the chapter dealing with the ovaries and testes, where a complete account will follow. Among the simplest types of mitosis, and those best adapted for laboratory study, at least as an approach to the subject, is that shown in the root tip of the dogtooth violet (Fig. 35, *a* to *n*). The cells and the mitotic figures are here so large that all the major details can be easily recognized by use of the usual dry, high-power lenses of the microscope.

PROPHASE.—This stage can again be subdivided into that of (*a*) the resting *nucleus (interkinesis)*; (*b*) the nucleus with *close spirem*; (*c*) the nucleus with the loose *spirem*; and (*d*) the *segmented spirem*. Coincident with these nuclear changes, the centrosome in animal cells divides into two (*diplosome*); these moieties move apart toward opposite poles of the nucleus and build a spindle (*amphiaster*) between themselves. Meanwhile the nuclear membrane begins to disappear, only a remnant distant to the achromatic spindle persisting at the end of the prophase. In the root tip cell of the dogtooth violet and in plant cells generally, the spindle appears in less conspicuous fashion than in animal cells. A centrosome is apparently lacking. The first indications of the spindle are the polar caps of faint radiations which grow medially to build the spindle. The *resting nucleus* (Fig. 35, *a*) is characterized by a random, granular reticulum with net
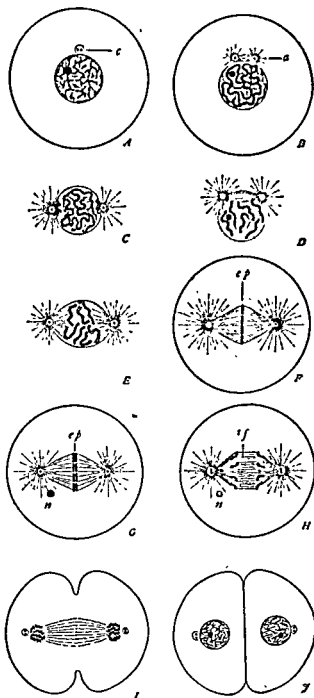
FIG. 33—SUCCESSIVE STAGES OF MITOSIS.

A-F, prophase; *G*, metaphase; *H*, anaphase; *I-J*, telophase *a*, achromatic spindle; *c*, centrosome; *ep*, equatorial plate of chromosomes; *if*, interzonal fibers; n, nucleolus (Wilson.)

knots and one or several nucleoli. This reticulum becomes changed into a delicate, deeply chromatic, probably continuous, *close spirem* (Fig. 35, *b*). By process of shortening and thickening, this changes into the *loose spirem stage* (Fig. 35, *c*).

The nucleoli have meanwhile contributed chromatic substance to the spirem, but may persist for some time longer as achromatic, ultimately fragmenting or dissolving, bodies. On closer inspection the close spirem is seen to consist of a series of granules (chromomeres); during the loose spirem stage these become split, thus giving rise to a double row of granules. The loose spirem passes into the succeeding stage (*segmented spirem*, Fig. 35, *d*) by transverse fission into a number of rods or *chromosomes*. At this stage all indication of chromomeres is generally again lost, the chromosomes appearing as compact, deeply staining rods.
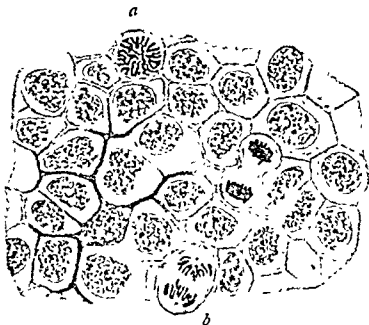

FIG. 34.—CELLS FROM EPIDERMIS OF THE SALAMANDER.

Three cells are in process of division by mitosis *a*, prophase; *b*, anaphase. The second cell above *b*, whose cell body is in process of fission, presents a stage of the telophase. (Wilson.)

The number of chromosomes is believed to be constant for all cells of a species. This belief rests upon data of actual counts in various insects and other lower animals and certain plant forms. Here the number is relatively small, and the individual chromosomes are large and can in consequence be readily counted. Attempts have been made repeatedly to throw doubt upon the matter of a specific chromosome constancy, but it is only fair to note that these attempts have dealt with relatively unfavorable material, where exact chromosome counts are difficult if not actually impossible. Also the chromosomes are generally believed to be the bearers of the determiners (genes) of hereditary characters.

METAPHASE.—This is a relatively brief stage in mitosis. It includes the period when the chromosomes are arranged upon the spindle in the *equatorial plate*. Seen in polar view this is called the *monaster stage* (Fig. 35, *e*). In this stage the chromosomes split longitudinally. In dogtooth violet the number of chromosomes is twenty-four. A common form of chromosome is the U-shaped type. The point of attachment to the spindle is the apex of the bent chromosome (Fig. 35, *f*). In the more rapidly growing cells the double or split condition of the chromosomes
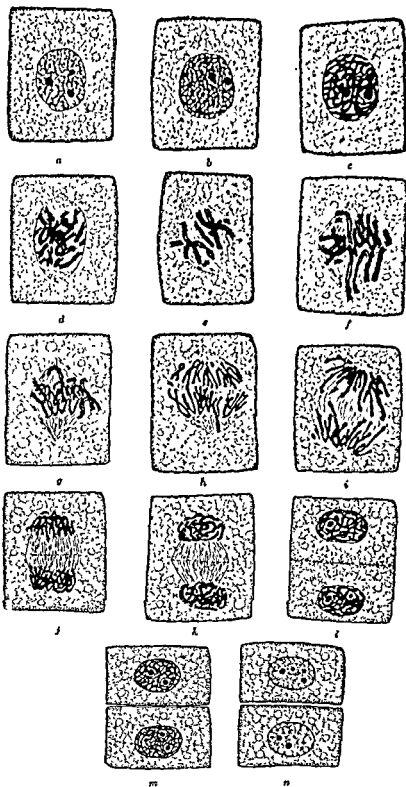
**FIG 35.—SUCCESSIVE STAGES OF MITOSIS IN THE ROOT TIP OF THE DOGTOOTH VIOLET
(ERYTHRONIUM AMERICANUM).**

a, resting nucleus; *b*, close spirem, *c*, loose spirem; *d*, segmented spirem; *e*, late prophase; *f* and *g*, metaphase; *h*, and *i*, anaphase; *j-l*, telophase (showing midbody or cell plate); *m* and *n*, daughter cells, *n*, with resting nuclei. ×1500
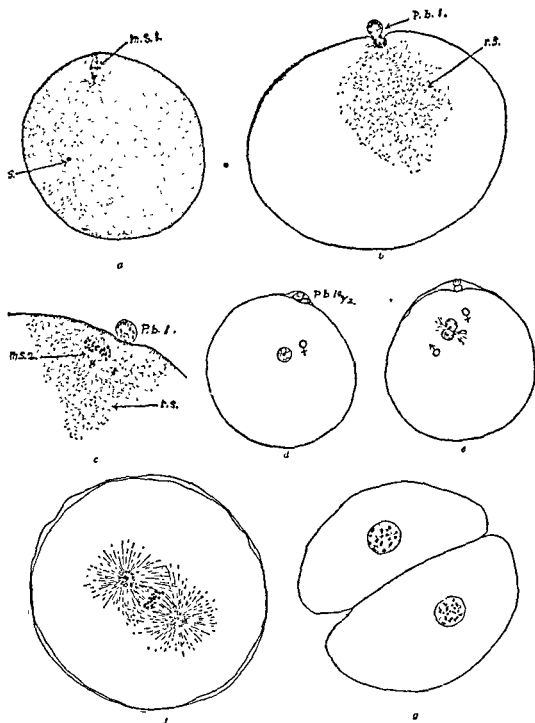
FIG 36—SUCCESSIVE STAGES IN THE MATURATION, FERTILIZATION AND SEGMENTATION OF
THE STARFISH (ASTERIAS FORBESII) EGG.

a, first maturation spindle (*m s 1*) and the spermatozoon (*s*); *b*, formation of the first
polar body (*p b 1*) and the residual substance of the nucleus (*r.s.*); *c*, second maturation
spindle (*m s 2*); *d*, female pronucleus (♀); *e*, union of male (♂) and female pronuclei
(the male pronucleus is derived from the spermatozoon); *f*, first segmentation spindle;
g, two-cell stage of division *d* and *e* are less highly magnified.

25

remained discernible since the preceding telophase, a true resting stage having n omitted. At metaphase the already longitudinally split chromosomes are comtely divided, and the separated moieties (daughter chromosomes) drawn' toward osite poles (Fig. 35, *g*).

ANAPHASE.—The limits of this phase are indefinite (Fig. 35, *h* to *j*). It may said to include all stages between that when the separation of the daughter omosomes, resulting from the longitudinal splitting of the mother chromosomes, severally consummated, and that when the groups of daughter chromosomes wn to either pole are still distinct. Seen in side or oblique view the later stage this phase present a double star arrangement of chromosomes—hence *diaster ge* (Fig. 35, *i*). The daughter chromosomes, an equal number at either pole, re drawn apart by activity of the outermost of the spindle fibers (called *mantle rs*), presumably by process of contraction. The inner or interzonal fibers conute the *central spindle*.

TELOPHASE.—Meanwhile a plate of granules (*cell plate; mid-body*) has appred in the equatorial region of the spindle. This marks the plane of the future ision (Fig. 35, *j* and *k*). In animal cells, an annular constriction appears pererally in the cell membrane. This proceeds centrally throughout telophase until imately the mother cell is divided into two daughter cells. The constriction of : cells in division is generally interpreted as a phenomenon of alteration in face tension. Coincidently with the steps of this process, the chromosomes and trosomes (archoplasm material in plants) pass through the stages of the proase, but in inverse order: segmented spirem, loose spirem, close spirem, resting ghter nucleus with its daughter centrosome and ultimately a nucleolus (Fig. , *k*, *l*, *m*, *n*). Where a cell plate appears, division is consummated without coniction. In certain pathological tissues, *e.g.*, cancers, the cells divide in various pical ways, involving the formation of tri- and multipolar spindles.

The time of the complete process of indirect cell division varies in different sues from one-half to several hours. In amphibian blood cells mitosis requires proximately two and one-half hours. W. H. and M. R. Lewis[17] studied the rision rate of the mesenchyma cells of the embryo chick. Tissue from embryos four to eleven days was cultivated in Locke's solution. The *total time required r a mitotic cycle varied from two to three hours. The prophase occupied from rty to sixty minutes; metaphase from two to ten minutes; anaphase from two three minutes; telophase from three to twelve minutes. The reconstruction period, : interval between the first appearance of the nuclear membrane and the attainnt of the normal resting condition of the daughter nuclei, covered from seventy one hundred and eighty minutes.* Strangeways[18] found that the time from the ginning of one division to the beginning of the next by one of the daughter cells s from 11 to 12 hours for embryonic chick cells in plasma plus embryonic extract.

17 Lewis, W. H and Lewis, M. R, 1917.
18 Strangeways, 1922

HISTOGENESIS

Every higher organism begins as a fertilized egg or zygote; this involves the fusion of a male (spermatozoon) and a female (egg) germ cell (Fig. 36, *a* and *c*). The result of the fusion is a mingling of approximately equal parts of paternal and maternal chromatin (presumably the basis of specific heredity), a large mass of maternal cytoplasm and nutritive substance with a small, but perhaps important mass of male cytoplasm; and a coincident stimulus to development. The fertilized egg divides by mitosis into two spheroidal cells—the typical embryonic form—or *blastomeres* (Fig. 36, *f* and *g*), and each of these again into two, the *cleavage*
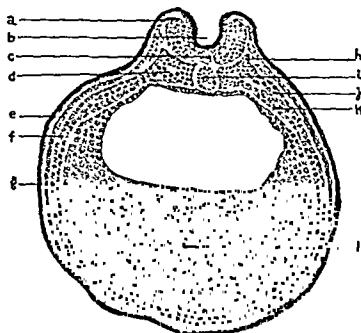

Fig 37.—Transverse Section of a Frog Embryo, Showing the Three Germ Layers.

a, neural crest; *b*, neural groove· *c*, neural plate; *d*, celom; *e*, ectoderm; *f*, mesoderm; *g*, entoderm; *h*, somite; *i*, notochord; *j*, parietal mesoderm; *k*, visceral mesoderm; *l*, yolk; central opening, the primitive intestine.

process continuing until the adult organism results as an aggregation of innumerable cells. This process of growth through cell multiplication is accompanied by cell differentiation, which constitutes *histogenesis*. The first outstanding stage in the differentiation is when the three fundamental germ layers: ectoderm (ectoblast; epiblast), mesoderm (mesoblast), entoderm (endoblast; hypoblast) appear (Fig. 37). Back of this must lie a more fundamental differentiation, perhaps already present in the unfertilized egg, a predelineation of adult structure destined to develop from localized egg materials. By histogenesis all the adult tissues arise from the several germ layers (see the following table):

has remained discernible since the preceding telophase, a true resting stage having been omitted. At metaphase the already longitudinally split chromosomes are completely divided, and the separated moieties (daughter chromosomes) drawn toward opposite poles (Fig. 35, *g*).

ANAPHASE.—The limits of this phase are indefinite (Fig. 35, *h* to *j*). It may be said to include all stages between that when the separation of the daughter chromosomes, resulting from the longitudinal splitting of the mother chromosomes, is severally consummated, and that when the groups of daughter chromosomes drawn to either pole are still distinct. Seen in side or oblique view the later stages of this phase present a double star arrangement of chromosomes—hence *diaster stage* (Fig. 35, *i*). The daughter chromosomes, an equal number at either pole, were drawn apart by activity of the outermost of the spindle fibers (called *mantle fibers*), presumably by process of contraction. The inner or interzonal fibers constitute the *central spindle*.

TELOPHASE.—Meanwhile a plate of granules (*cell plate; mid-body*) has appeared in the equatorial region of the spindle. This marks the plane of the future division (Fig. 35, *j* and *k*). In animal cells, an annular constriction appears peripherally in the cell membrane. This proceeds centrally throughout telophase until ultimately the mother cell is divided into two daughter cells. The constriction of the cells in division is generally interpreted as a phenomenon of alteration in surface tension. Coincidently with the steps of this process, the chromosomes and centrosomes (archoplasm material in plants) pass through the stages of the prophase, but in inverse order: segmented spirem, loose spirem, close spirem, resting daughter nucleus with its daughter centrosome and ultimately a nucleolus (Fig. 35, *k*, *l*, *m*, *n*). Where a cell plate appears, division is consummated without constriction. In certain pathological tissues, *e.g.*, cancers, the cells divide in various atypical ways, involving the formation of tri- or multipolar spindles.

The time of the complete process of indirect cell division varies in different tissues from one-half to several hours. In amphibian blood cells mitosis requires approximately two and one-half hours. W. H. and M. R. Lewis[17] studied the division rate of the mesenchyma cells of the embryo chick. Tissue from embryos of four to eleven days was cultivated in Locke's solution. The total time required for a mitotic cycle varied from two to three hours. The prophase occupied from thirty to sixty minutes; metaphase from two to ten minutes; anaphase from two to three minutes; telophase from three to twelve minutes. The reconstruction period, the interval between the first appearance of the nuclear membrane and the attainment of the normal resting condition of the daughter nuclei, covered from seventy to one hundred and eighty minutes. Strangeways[18] found that the time from the beginning of one division to the beginning of the next by one of the daughter cells was from 11 to 12 hours for embryonic chick cells in plasma plus embryonic extract.

17 Lewis, W. H. and Lewis, M. R., 1917.
18 Strangeways, 1922

CYTOMORPHOSIS

From the standpoint of the individual cells of tissues, histogenesis involves progressive and regressive changes. This process may be designated as *cytomorphosis* (Minot). The gradual acquirement of definite form by development is known as *morphogenesis*. Cytomorphosis includes several successive steps: (*a*) undifferentiated or embryonal stages; (*b*) differentiated stage, during which the cell acquires and maintains its maximum differentiation—expressed structurally by a definite shape and specific content—and performs its specific function; (*c*) regressive, when the function gradually wanes, and finally fails (reflected in coincident protoplasmic alterations), the cell concerned suffering death and ultimately removal from the body.

With this preliminary general view of protoplasmic organization and function (general cytology) we are prepared to approach histology proper.

Adult Tissue Derivatives

ECTODERM	MESODERM	ENTODERM

ECTODERM

Epidermis and its derivatives: hair, nails, and epithelium of sebaceous, sweat and mammary glands.

Epithelium of mouth and its derivatives: enamel, taste buds, epithelium of salivary and other buccal glands, and anterior portion of hypophysis.

Epithelium of anus, and distal portion of the male urethra.

Epithelium of nostrils and communicating glands and cranial sinuses.

Epithelium of conjunctiva and associated ducts and lacrimal glands. The lens, and the epithelium of the pars nervosa, ciliaris and iridica retinae.

Epithelium of membranous labyrinth of internal ear, and lining of external ear.

Epithelium lining the central canal of the spinal cord, and the ventricles of the brain.

All neurons and neuroglia of the nervous system.

Certain ductless glands: pineal, posterior (nervous) portion of hypophysis, medulla of suprarenal, and the chromaffin system or paraganglia.

Possibly smooth muscle associated with sweat glands, and in iris of eye.

MESODERM

Epithelium of uriniferous tubules, renal pelves and ureters.

Epithelium of the seminiferous tubules and the associated excretory ducts of the testis; epithelium of oviduct and uterus; probably also the sex cells. The cortex of the suprarenal gland. All muscular tissue; connective tissue; vascular tissue (blood and lymph vessels and cells), and lymphoid organs in general.

Epithelium (mesothelium) of pleurae, pericardium and peritoneum; of the tendon sheaths, joint cavities and bursae; and of the chambers of the eye, and the perilymph spaces of the internal ear (scalae tympani and vestibuli).

ENTODERM

Epithelium of digestive tract (including pharynx; excluding mouth and anus) and associated glands: pharyngeal, esophageal, gastric, intestinal, pancreas and liver, with gallbladder.

Epithelium of middle ear (tympanum) and auditory (eustachian) tube. Epithelium of respiratory system, beyond nostril. Epithelium of thyroid, parathyroids, and the thymic reticulum and corpuscles.

Epithelium of female urethra, proximal part of male urethra, and of the urinary bladder.

Epithelium of prostatic and Cowper's glands in the male, and of the glands of Bartholin in the female.

Nuclei pulposi of intervertebral disks, remains of the embryonic notochord. (Of ectodermal origin in the guinea-pig according to G. Carl Huber, *Anat. Rec*, 1918, 14. Of mesodermal origin, according to H. Triepel; *Anat. Hefte*, 1914, 50.)

CYTOMORPHOSIS

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With this preliminary general view of protoplasmic organization and function (general cytology) we are prepared to approach histology proper.

CHAPTER II

TISSUES

A tissue in the histologic sense is a collection of similarly specialized cells united in the performance of a particular function, *e.g.*, liver tissue. In certain tissues the cells are joined together by an *intercellular cement substance*, which is a secretion product of the cells themselves. Through this cement may extend the so-called

"intercellular bridges" or cytodesmata, the minute intervening spaces forming delicate canaliculi, presumably for mediating the transfer of nutritive material from cells more favorably placed with respect to the source of supply to those less favorably located, *e g.*, epidermis; these bridges arise through process of vacuolization in the exoplasm of adjoining cells, the walls of the original vacuoles per-

sisting as bridges. Through such bridges, fibrils may extend from cell to cell. Practically every tissue contains also connective tissue elements for unification and support; also vascular and nervous constituents. Tissues in which the cell boundaries are absent are known as *syncytia* (Fig. 39). A syncytium may obviously arise

FIG 39—A VILLUS OF THE HUMAN PLACENTA, SHOWING A PERIPHERAL SYNCYTIUM OF IRREGULAR THICKNESS.

The connective tissue inclosed by the syncytium contains three capillary vessels. Hematein and eosin. ×500.

FIG. 40.—CELLS FROM THE PANCREAS OF NECTURUS, CONTAINING SECRETORY GRANULES AND BASAL ERGASTOPLASMIC FILAMENTS. (Matthews.)

through nuclear proliferation in the absence of cytoplasmic division, or as the result of the disappearance of original cell boundaries. We may distinguish the following fundamental tissues: (*a*) epithelial; (*b*) connective; (*c*) muscular; (*d*) nervous; and (*e*) vascular.
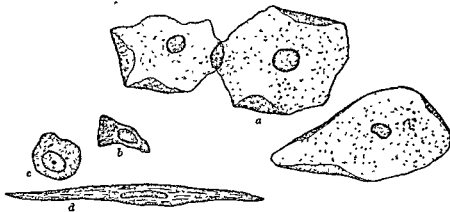

FIG 41.—VARIOUS FORMS OF CELLS.

a, squamous epithelium from the tongue; *b*, a columnar cell from the small intestine; *c*, a polyhedral or spheroidal cell from the liver; *d*, a smooth muscle cell from the muscular coat of the stomach. ×550.

Lymphoid tissue may be regarded as still another fundamental tissue; or it may be included under vascular tissue. In fact from the genetic viewpoint, vascular may be included under connective tissue, since both arise from the mesenchyma.

Representatives of all of the fundamental tissues are generally found in all histologic preparations, or tissues in a general sense. Cells vary greatly both from the standpoints of shape and contents in the various tissues—both depending upon the types and phases of function. The more usual form variations include: (*a*) spheroidal, spherical (*e.g.*, embryonic cells and egg cells, Fig. 1), polyhedral (spherical cells modified by pressure from adjacent cells, *e.g.*, liver cells, Fig. 42) ; (*b*) scale-like or squamous (*e.g.*, superficial cells of mucous membrane of mouth, Fig. 41, *a*) (*c*) columnar, prismatic or cylindrical (*e.g.*, cells lining intestine). Columnar cells, when very short, are usually designated *cubical* or *cuboidal* (*e.g.*, bronchioles and rete testis, Fig. 48); intermediate lengths may be designated either tall cuboidal or short columnar ; when modified by confinement in an alveolus into a pyramidal shape as in glands, they may be called pyramidal or glandular (Fig. 57). Glandular cells, moreover, are characterized also by an internal differentiation commonly expressed in the form of granules or filaments. Columnar cells may be further modified by the appearance of cilia into ciliated epithelium (*e.g.*, trachea, bronchial tube, Fig. 57), or of mucus into goblet cells or unicellular glands (*e.g.*, intestine) ; or as specialized receptors for stimuli of special sense they may become modified as neuro-epithelium (*e.g.*, certain cells of eye, nose and tongue).
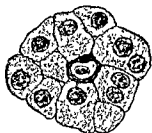
FIG. 42.— POLYHEDRAL EPITHELIUM, FROM A SECTION OF THE HUMAN LIVER.

The central blood capillary contains one leukocyte, and its wall contains the nucleus of a flattened endothelial cell. ×550.

EPITHELIAL TISSUES

Epithelia are cellular membranes covering the surfaces and lining the internal cavities of the body. They serve for protection, secretion, excretion, absorption, and the reception of stimuli. The constituent cells may be of any of the above enumerated forms. The spheroidal types, however, are found only in embryonal membranes The term spheroidal epithelium is sometimes employed to designate masses or solid columns of spheroidal cells, such as appear in the sex cords of the developing testis and ovary, and in the early stages of glands. They are, in general, outgrowths or evaginations from embryonic or undifferentiated epithelia.

An epithelium may consist of a single layer of cells, when it is called nonstratified or *simple epithelium*. A complete description, however, must include the name of the preponderating type of cell, *e g.*, simple columnar epithelium, or simple squamous epithelium, as the case may be. Moreover, an epithelium may consist of several or many layers, when it becomes a *complex* or *stratified epithelium* The uppermost type of cells gives the name to stratified epithelium ; for example, in the epidermis the outermost cell is of the squamous type, though the middle cells are polyhedral, and the innermost columnar ; hence called stratified squamous epithelium (Fig. 54).

In the stratified epithelia the superficial cells arise through cell division in the deeper layers, and if they become detached by abrasion, disintegration, or by other physiological or pathological processes, they may be replaced by cell reproduction occurring in the lower layers. When but a single layer of cells is present, as in
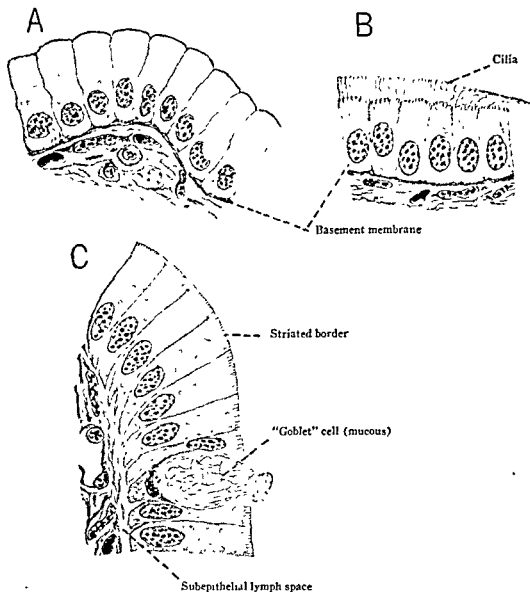

FIG 43—SIMPLE COLUMNAR EPITHELIUM.

A, from the human prostate; *B*, ciliated, from the human oviduct; *C*, from longitudinal section of a villus of the human small intestine. (Hardesty.)

the simple epithelia, loss of cells over large areas will obviously become more difficult of replacement by cell division. Hence it is that repair of extensively destructive pathological conditions involving such epithelial tissues becomes exceedingly difficult and often impossible, as, for example, in the alveoli of the lung.

Representatives of all of the fundamental tissues are generally found in all histologic preparations, or tissues in a general sense. Cells vary greatly both from the standpoints of shape and contents in the various tissues—both depending upon the types and phases of function. The more usual form variations include: (a) spheroidal, spherical (e.g., embryonic cells and egg cells, Fig. 1), polyhedral (spherical cells modified by pressure from adjacent cells, e.g., liver cells, Fig. 42); (b) scale-like or squamous (e.g., superficial cells of mucous membrane of mouth, Fig. 41, a) (c) columnar, prismatic or cylindrical (e.g., cells lining intestine). Columnar cells, when very short, are usually designated cubical or cuboidal (e.g., bronchioles and rete testis, Fig. 48); intermediate lengths may be designated either tall cuboidal or short columnar; when modified by confinement in an alveolus into a pyramidal shape as in glands, they may be called pyramidal or glandular (Fig. 57). Glandular cells, moreover, are characterized also by an internal differentiation commonly expressed in the form of granules or filaments. Columnar cells may be further modified by the appearance of cilia into ciliated epithelium (e.g., trachea, bronchial tube, Fig. 57), or of mucus into goblet cells or unicellular glands (e.g., intestine); or as specialized receptors for stimuli of special sense they may become modified as neuro-epithelium (e.g., certain cells of eye, nose and tongue).

FIG. 42.—POLYHEDRAL EPITHELIUM, FROM A SECTION OF THE HUMAN LIVER.

The central blood capillary contains one leukocyte, and its wall contains the nucleus of a flattened endothelial cell. ×550.

EPITHELIAL TISSUES

Epithelia are cellular membranes covering the surfaces and lining the internal cavities of the body. They serve for protection, secretion, excretion, absorption, and the reception of stimuli. The constituent cells may be of any of the above enumerated forms. The spheroidal types, however, are found only in embryonal membranes. The term spheroidal epithelium is sometimes employed to designate masses or solid columns of spheroidal cells, such as appear in the sex cords of the developing testis and ovary, and in the early stages of glands. They are, in general, outgrowths or evaginations from embryonic or undifferentiated epithelia.

An epithelium may consist of a single layer of cells, when it is called non-stratified or simple epithelium. A complete description, however, must include the name of the preponderating type of cell, e.g., simple columnar epithelium, or simple squamous epithelium, as the case may be. Moreover, an epithelium may consist of several or many layers, when it becomes a complex or stratified epithelium. The uppermost type of cells gives the name to stratified epithelium, for example, in the epidermis the outermost cell is of the squamous type, though the middle cells are polyhedral, and the innermost columnar; hence called stratified squamous epithelium (Fig. 54).

Classification

I. Simple (Nonstratified) Epithelia—those which compose a membrane but one cell in thickness. Epithelial cells, usually spherical or polyhedral in shape, occur also *en masse* in the form of cords or clusters.

1. Squamous, composed of flattened, scale-like cells

    (a) Lining closed cavities

    Pavement epithelium

    or (1) *endothelium*, heart, arteries, capillaries, veins, and lymphatic vessels

    (2) *mesothelium*; serous membranes

    (3) *mesenchymal epithelium*, synovial membranes, bursae, and tendon sheaths, lining of the anterior chamber of the eye, and of the perilymph spaces of the internal ear, and of the subdural and subarachnoid spaces of the brain and spinal cord

    (b) Lining the alveoli of the lungs, some tubules of the kidney, the middle ear, and the membranous labyrinth of the internal ear

    (c) As the superficial cells of stratified epithelium (*vide infra*)

2. Columnar

(A) Plain

    (a) Lining the mucous membrane of the alimentary tract—stomach, small intestines, large intestines, gallbladder

    (b) Lining the ducts of all secreting glands—liver, pancreas, salivary, lacrimal, and mammary glands, testicle, prostate, kidney, etc.

    (c) The deepest layer of cells in stratified epithelium is composed of columnar-shaped cells, which, however, differ in structure from the true columnar type

(B) Modified

(1) Ciliated

    (a) Lining the uterus and oviducts

    (b) Lining portions of the ventricles of the brain and central spinal canal of the embryo and infant—in later life these cells lose their cilia

(2) Pyramidal or glandular

    The secreting cells of all tubular glands—kidney, pancreas, salivary glands, intestinal glands, etc.

(3) Goblet[1]

    (a) *Respiratory tract*—nasal, pharyngeal, tracheal, and bronchial mucous membranes

    (b) *Alimentary tract*—small and large intestines

(4) Neuro-epithelium

    (a) *Eye*—the rod and cone cells of the retina

    (b) *Ear*—in the cristae and maculae of the labyrinth and in Corti's organ

    (c) *Nose*—in the olfactory mucous membrane (true neuron)

    (d) *Tongue*—in the taste buds

---

[1] Cells whose protoplasm has been converted into mucinogen They may be considered unicellular, mucus-secreting glands.

Each epithelial cell is to some extent a secreting cell. Sometimes secretion is its chief function, as is the case with goblet cells, which might well be called unicellular glands, and which secrete abundant mucus. The same is true of those cells which form the parenchyma of secreting glands—salivary glands, kidney, and liver. In many epithelia secretion is a subsidiary function, protection being the primary purpose.

In all epithelia a cement substance is present between the cells. This becomes especially abundant and dense between the distal ends of the cells of columnar epithelium, and is here known as *terminal bars* (Fig. 45). Cement substance has
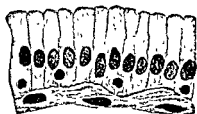

FIG. 44 — COLUMNAR EPITHE- LIUM FROM THE PYLORIC RE- GION OF THE HUMAN STOM- ACH.
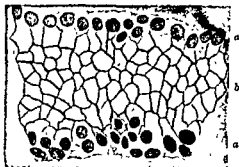
Profile view. Hematein and eosin ×550.

FIG. 45.—"TERMINAL BARS" OF CE- MENT SUBSTANCE AS SEEN BETWEEN THE EPITHELIAL CELLS OF A TUBU- LAR SECRETING GLAND IN THE PY- LORIC REGION OF THE HUMAN STOMACH.

The columnar epithelium is seen in profile at *a*; at *b*, the free ends of the cells are seen. ×550.

the peculiar property of precipitating silver nitrate from solutions, which turns black on exposure to sunlight. This furnishes an especially favorable technic for demonstrating cell boundaries. All epithelia, simple or stratified, rest upon a homo- geneous basement membrane or *membrana propria*, the joint product of the cells themselves and the underlying connective tissue, and a subjacent connective tissue supporting membrane or *lamina (tunica) propria* (or *corium*). The latter only contains blood and lymph vessels, from which the epithelial cell must draw nourish- ment by process of absorption, and transfer through "intercellular bridges." It furnishes support also for the nerve supply. We may now consider briefly the usual types of simple and stratified epithelia. The main facts are summarized in the outline on page 35:

scalae tympani and vestibuli of the internal ear, and the subarachnoid and subdural spaces of the brain and spinal cord. These cavities arise as splits, or by the union of isolated spaces, in the mesenchyma, the mesenchymal lining cells taking on epithelioid characters and arranging themselves in the form of a membrane. The most satisfactory disposition of this group of epithelia seems to be to classify them as false or mesenchymal epithelia.

Such epithelia have been experimentally produced by the introduction of small sheets of colloidin and masses of paraffin into the subcutaneous tissue and cornea respectively, of laboratory animals; the connective tissue cells became changed into large flat cells, disposed in the manner of a mesothelium. These results suggest the conclusion that the mesothelial cells of pleura, pericardium and peritoneum may be regenerated in the event of destruction from exposed connective tissue cells of the subepithelial stroma.[3]

The individual squamous cells are flat plates bulging at the center where the oval nucleus is located, with serrated borders. In surface view the endothelial cell is oblong, the long axis parallel with the long axis of the vessel (Fig. 46), while the mesothelial cell is polygonal in outline (Fig. 47). In sections through the nucleus, these cells in side view present a flat spindle-shaped appearance.

Mesothelia exhibit small intercellular spaces, the *stigmata* They have been regarded as openings between the body cavities and lymph spaces and vessels; but are more probably transient structures, perhaps artifacts. Abdominal mesothelial of lower forms, *e g*, frog, contain also permanent openings, or *stomata*, surrounded by specialized *guard cells.*

FIG. 46. — ENDOTHELIUM LINING A LARGE ARTERY.

The mesenchymal epithelial cells of synovial membranes vary greatly in shape according to the degree of pressure to which they are subjected. They may thus be of the cuboidal or the squamous type; and they may even become pressed apart so as to expose the underlying connective tissue.

Simple Columnar Epithelium.—*Plain.*—This type of epithelium consists of columnar or cylindrical elements (Fig 44), in transverse section presenting polygonal, frequently hexagonal, outlines (Fig. 45). It may be tall, medium or low columnar epithelium, depending upon the height of the individual cell of the particular membrane. The lower types may be designated cuboidal epithelia (Fig. 48). The phenomenon of *polarity* is particularly well exhibited by a tall columnar cell, a condition inhering in a structural and functional differentiation between the attached, or *proximal,* and the free, or *distal,* end of the cell, dependent in a
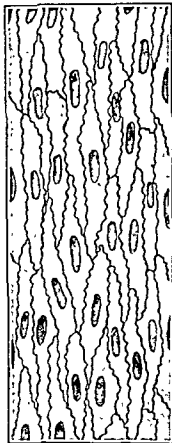
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[3] Clarke, 1914.

II. Complex (Stratified) Epithelia—those whose cells form several superimposed layers.

1. Squamous	Superficial cells, *squamous*; deeper, *polyhedral*; the deepest, *columnar* in shape	Forms the epidermis of the skin, and covers the free surface of those mucous membranes which clothe all orifices in direct connection therewith—*viz.*, the conjunctiva and cornea; the external auditory canal; part of the nasal mucous membrane; mouth, pharynx, and esophagus; epiglottis and vocal cords; anus, as high as the internal sphincter; vagina and external portion of the urethra
2. Columnar (pseudo-stratified columnar)	Superficial cells, *columnar*; deeper cells, *polyhedral* or *spindle-shaped* (a) *Nonciliated* (rare) (b) *Ciliated*	(a) Part of ductus deferens (b) Respiratory tract; nasal mucous membrane and passages connected therewith, tear ducts, auditory tube, etc., larynx, trachea, and bronchi Male genital tract; epididymis and ductus deferens
3. Transitional	*Superficial cells,* only somewhat *flattened;* next deeper layer, *pear-shaped,* deepest layers, *polyhedral*	Found only in the *urinary system—viz.*, pelvis of the kidney, ureter, bladder, and first portion of the urethra

Nonstratified Epithelia

Simple Squamous Epithelium (Pavement Epithelium).—This variety of epithelium comprehends two main groups: the *endothelia*, lining the vascular system, and the *mesothelia* of the serous membranes lining the large internal closed cavities—pleurae, pericardium and peritoneum This distinction is somewhat arbitrary but nevertheless useful, and derives justification in that endothelia arise in the first instance from syncytial mesoderm (mesenchyma) and mesothelium from epithelial mesoderm

But according to Bremer [2] at least some of the earliest blood vessels in man also arise from true mesothelial cells. Mesothelium lines the extra-embryonic body cavity and is reflected over the yolk sac and body stalk. In the latter location Bremer describes ingrowths of mesothelium into the mesenchyma from which endothelium and blood cells develop.

This classification should include also another group of closed cavities, namely, the tendon sheaths, bursae, joint or synovial cavities, chambers of the eye, the

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[2] Bremer, 1914.

may differentiate into goblet cells, the process involving loss of the cilia. The undulatory movement of the vibratile cilia is always in the same direction, i.e., towards the external surface of the body. The coördinated movement of the cilia in a definite direction serves to carry the mucus with its adherent dust and débris toward the exterior. Each cell contains from 20 to 30 cilia. The cilia move automatically, their coordination throughout the ciliated area being effected by a protoplasmic continuity between adjacent cells mediating a primitive type of nervous activity, designated "neuroid transmission." The cilia move from 12 to 20 times a second.

The second chief type of ciliated epithelium, i.e., that with nonmotile cilia, is found best represented in the duct of the epididymis. These cilia lack basal granules. Ciliary motility is apparently dependent upon attachment to centrosomal (basal) granules. These cells divide at first only by mitosis; after the assumption of secretory activity, by amitosis The function of nonmotile cilia is related to the process of the elimination of secretions. The "brush borders" of the cells of the convoluted tubules of the kidney, and the "striated borders" of the plain columnar cells of the gastro-intestinal tract, are less highly developed analogous structures. These pseudocilia (stereocilia) represent spongioplastic remnants of the distal borders of cells altered during secretory or absorptive activity.

FIG 49.— COLUMNAR CELL IN PROCESS OF CILIOGENESIS.

From the hydatid of Morgagni; showing the partition of the centrosome and the migration of the resulting basal bodies to the distal surface where cilia are sprouted. ×2000. (From Walter, Anat Rec., 1929, 42:2.)

GLANDULAR EPITHELIUM.—This type derives its name from the fact of the predominance of the glandular function. This condition is structurally expressed in a segregation of the presecretion bodies (granules, rods, threads) in the basal end of the cell, and of the secretion products (granules, spherules, and mucous or serous fluid) in the distal end (Fig. 40). Morphologically it represents simply a modified columnar cell, its pyramidal shape resulting from mechanical factors due to its disposition in saccular or spherical acini, the periphery of the central lumen of which is much less than the periphery of the acinus, necessitating the modification in shape of the individual cells (Fig. 46). The cells of glandular epithelium usually lack cuticular borders. Pyramidal or glandular epithelium is found in tubules of the kidney, salivary glands, the pancreas, in the secreting glands of the gastric and intestinal mucous membrane, in the mucous glands of the esophagus, pharynx, bronchial tubes and oral and nasal cavities, and in the secreting glands of the skin.

GOBLET-CELL EPITHELIUM.—A further important and widespread modification of columnar cells in epithelia concerns the elaboration and storage of mucous
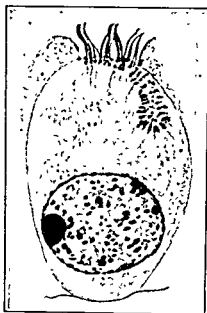
final analysis in larger measure upon distance from source of the nutritive and oxygenative stream in the blood. The nucleus is generally located nearer the proximal end; this end, moreover, tapers to a point and is occasionally bifid; and it contains the presecretion (ergastoplasm, prozymogen, etc.) granules, rodlets and fibrils in secreting epithelia (Fig. 40). The distal border is frequently striated (cuticular
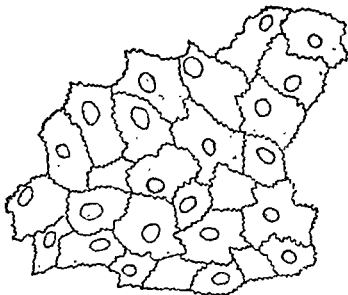

FIG. 47.—MESOTHELIUM, SURFACE VIEW, FROM THE MESENTERY OF A RAT.

Silver nitrate and hematein ×550

margin, striated border), an appearance due to the presence of minute canals, or more frequently, short pseudopodia, mediating absorption or the elimination of secretion. Striated borders are particularly prominent in the columnar cells of the intestine. In the secreting cells of the kidney the marginal processes are more prominent and divergent, forming "brush borders." Where the cell mem-

FIG. 48.—CUBOIDAL EPITHELIUM FROM THE RETE TESTIS OF THE RABBIT.

a, epithelium; b, connective tissue. Hematein and eosin. ×550

brane becomes greatly thickened on the free surface of a columnar cell, it is termed a *crusta*. Also, in neuro-epithelial cells, the free border mediates reception, the attached pole transmission of stimuli.

Modified Columnar Epithelium.—CILIATED EPITHELIUM.—This occurs in two distinct forms: (a), that in which the hair-like processes or cilia are vibratile; (b), that in which the cilia are nonmotile. In the former case the cilia are attached to a double row of *basal granules*, ranged along the distal border of the columnar cell. In development the cilia sprout from these granules. The basal bodies are partition products of the centrosome. Such ciliated cells divide only by amitosis. They

The accumulation of mucus (mucinogen) within the cytoplasm expands the cell, finally ruptures its walls in the direction of least resistance, and thus permits its mucous content to exude upon the free surface, leaving behind the small glandular protoplasmic cell remnant attached to the basement membrane. The
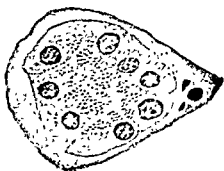

FIG. 51.　　　　　　　FIG. 52.

FIG. 51.—A GROUP OF CELLS FROM A TRANSECTION OF AN ACINUS OF THE HUMAN PANCREAS; GLANDULAR EPITHELIUM.
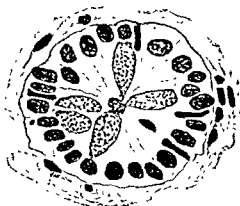
Hematein and eosin. ×550.

FIG. 52.—GOBLET CELLS AS SEEN IN A TRANSECTION OF A CRYPT OF THE LARGE INTESTINE OF MAN.

Sections of five goblet cells are seen among the columnar cells which line the tubule. Muchematein and eosin. ×550.

further history of these cell remnants is somewhat doubtful. They are possibly resorbed or removed, and finally replaced through mitotic division of adjacent cells. There is, however, some evidence to show that after function they are still capable of further growth whereby they may regain their original form and become again able to pass through the same stages of secretory activity.

NEURO-EPITHELIUM.—The cells of neuro-epithelium are columnar elements specially differentiated to form nerve end-organs. They are usually elongated cells having a bulging nucleated center, their free extremity either projecting beyond the epithelial surface as a bundle of fine cilia or as a slender nonciliated process which terminates within a pore-like opening directly connected with the free surface. Their attached extremity, tapering to a fine process, is in relation with the terminal arborization of the axis cylinder of a nerve fiber. Neuro-epithelium is found only in the several organs of special sense, and will be more fully described as a part of these several organs.
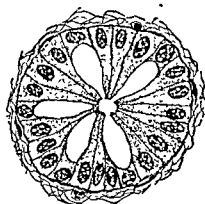

FIG. 53.—DIAGRAM SHOWING THE ARRANGEMENT OF THE COLUMNAR AND GOBLET CELLS OF FIGURE 52.

The goblet cells are represented as being empty; their unaltered basal portions containing the nucleus are distinctly seen.

secretion, giving to the loaded cells a goblet form (Figs. 52, 53). Goblet cells
may occur among either the plain or ciliated columnar cells. They are most
abundant in the intestinal tract but are also to be found in the bronchial tubes,
trachea, nasal mucous membrane, and in the ducts and tubules of mucus secreting
glands. In such epithelial membranes certain columnar cells, if not indeed all
of these cells, are destined to secrete mucus. The cytoplasm of such cells is con-
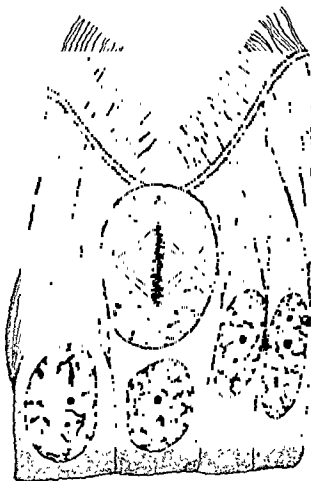

FIG. 50.—CILIATED CELLS FROM INTESTINE OF THE MUSSEL, CYCLAS.

The cells have a double row of basal granules, with cilia attached to the distal row, rootlets
(tonofibrils) to the proximal row. The medial cell, in mitosis, lacks cilia. ×2300 (Helvestine.)

verted into a glairy mass of a peculiar vitreous appearance, which occupies an
increasing proportion of the free extremity of the cell. This "mucinogen," when
acted upon by alcohol, is precipitated within the cell, and then forms fine basophilic
fibrils or granules which stain deeply with the muchematein and mucicarmine
solutions of P. Mayer. At the base of the goblet cell, its nucleus is embedded
in a minute mass of unaltered granular cytoplasm.

The accumulation of mucus (mucinogen) within the cytoplasm expands the cell, finally ruptures its walls in the direction of least resistance, and thus permits its mucous content to exude upon the free surface, leaving behind the small glandular protoplasmic cell remnant attached to the basement membrane. The
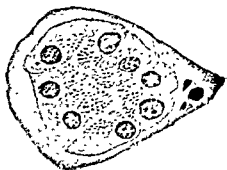

FIG 51.   FIG. 52.

FIG. 51.—A GROUP OF CELLS FROM A TRANSECTION OF AN ACINUS OF THE HUMAN PANCREAS; GLANDULAR EPITHELIUM.
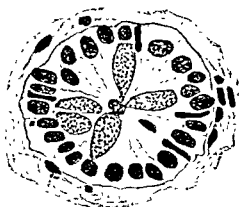
Hematein and eosin. ×550.

FIG. 52.—GOBLET CELLS AS SEEN IN A TRANSECTION OF A CRYPT OF THE LARGE INTESTINE OF MAN.

Sections of five goblet cells are seen among the columnar cells which line the tubule. Muchematein and eosin. ×550.

further history of these cell remnants is somewhat doubtful. They are possibly resorbed or removed, and finally replaced through mitotic division of adjacent cells. There is, however, some evidence to show that after function they are still capable of further growth whereby they may regain their original form and become again able to pass through the same stages of secretory activity.

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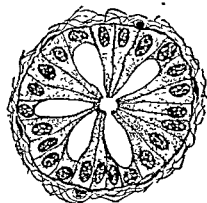

FIG. 53.—DIAGRAM SHOWING THE ARRANGEMENT OF THE COLUMNAR AND GOBLET CELLS OF FIGURE 52

The goblet cells are represented as being empty; their unaltered basal portions containing the nucleus are distinctly seen.

STRATIFIED EPITHELIUM

Stratified Squamous Epithelium.—This variety of epithelium occurs as a membrane of varying thickness but always comprising several cell layers. A straight line perpendicular to its free surface would penetrate from five to thirty or more epithelial cells. But while there is a wide diversity in the thickness of the epithelial layers, the character of the cells at any given level is very nearly constant. Thus the deeper cells, those nearest the basement membrane, are nucleated, of soft consistence and may contain mitotic figures, indicating that it is at this level that cell reproduction is most active. Toward the surface of the membrane
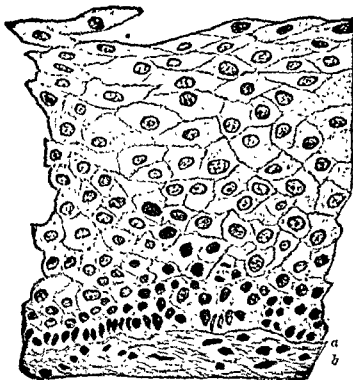

FIG. 54.—STRATIFIED SQUAMOUS EPITHELIUM FROM THE HUMAN ESOPHAGUS.
a, basement membrane; *b*, connective tissue. Hematein and eosin ×410

the cells become progressively of firmer consistence, so that the most superficial ones present a horny appearance as a result of the gradual keratization of the cytoplasm during the progress of the cell toward the surface. The keratization is apparently dependent upon surrounding physical conditions, for it is much more marked in the skin, which from constant and rapid evaporation is comparatively dry, than in the mouth, esophagus, or conjunctiva, where the epithelium is constantly moistened by glandular secretions; the margins of the lips, eyelids, etc., present an intermediate state of keratization.

With these chemical changes in the composition of the cytoplasm there are corresponding changes in its nucleus. In the deeper cells, the nucleus is oval

or spherical and highly chromatic. Toward the surface, the nucleus becomes more and more flattened and more and more obscured by the cornification of the cell protoplasm. In the most superficial cells it is usually impossible to demonstrate the nuclei, except by acting upon their protoplasm with strong reagents such as caustic alkalis, soda or potassa.

But the most characteristic change in the cells of stratified epithelium is the progressive transition in shape undergone during their passage from the deeper layers to the free surface. New cells, resulting from indirect division of the cells in the deeper layers, are by continued reproduction gradually pushed toward the surface, whence they are constantly being desquamated in small scaly masses. The
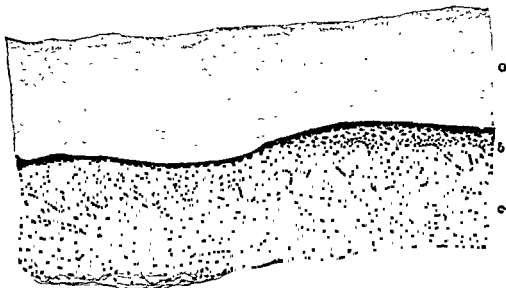

FIG 55.—EPIDERMIS OF THE SKIN OF THE FINGER TIP, SHOWING EXTREME KERATIZATION OF THE EPITHELIUM

a, keratized epithelium, b, malpighian or germinal layer, c, connective tissue Hematein and eosin × 50.

pressure exerted in this process tends to gradually flatten these cells so that their vertical diameter, that perpendicular to the surface, becomes progressively shorter the nearer they approach the free surface; on the other hand, their transverse diameter, that parallel to the surface of the epithelial membrane, is correspondingly increased. The deepest cells of the stratified epithelium—those which rest upon the basement membrane—are elongated in their vertical diameter and possess an irregularly columnar shape. Their nuclei are likewise elongated, oval or elliptical in shape. In the skin of brunettes and the dark-skinned races, and in the epithelium of the skin of the scrotum, perianal region, and areolae of the breasts, these cells contain small granules of the pigment to which the color of the cuticle is largely due. This columnar cell layer is then described as the layer of pigment epithelium. Superficial to these, but still in the deeper layers, are polyhedral cells with spherical nuclei, which are known as *prickle cells* because of their prominent intercellular bridges. Superficial to the prickle cells, the epithelial cells become

progressively more flattened, until at the surface, they are mere scales. This gradual transition from columnar and polyhedral cells below, to thin flat scales on the surface is characteristic of all stratified epithelium.

The thin superficial scales resemble very closely in shape and appearance the squamous epithelium previously described. The deeper cells have a finely granular cytoplasm and distinct nuclei except when obscured by the appearance of keratin within their protoplasm. Many of these cells contain coarse granules of *eleidin* and *keratohyalin*—substances chemically intermediate between the unaltered and keratized protoplasm.

FIG 56 — PSEUDOSTRATIFIED COLUMNAR CILIATED EPITHELIUM FROM A BRONCHIAL TUBE OF MAN.

a, a goblet cell; *b*, cilia; *c*, superficial cytoplasmic layer, the nuclei of the columnar cells are somewhat more deeply stained than those of the basal cells; *e*, basement membrane; *f*, connective tissue. Hematen and eosin. ✕550.

As stated, the formation of *keratin* within these cells is more active in those membranes which are comparatively dry from exposure to the air. Consequently, it is most active in the epidermis of the skin. If stratified epithelium is at all times well moistened, as, for example, in the mouth and esophagus, the formation of keratin is slight, and the soft polyhedral cells compose the major portion of the epithelial membrane which then has only a thin superficial covering of flattened scaly cells. In the comparatively dry epidermis, on the other hand, the flattened horny cells frequently occupy more than half the thickness of the epithelial layer (Fig. 55).

In the superficial squamous cells of moist membranes the nucleus can always be readily demonstrated, even in the keratized cells of the extreme surface. Cells of the intermediate layers, especially those just above the prickle layer, frequently show nuclei in process of amitotic division. This condition is presumably associated with an early stage of degeneration dependent upon a scarcity of nutriment due to the relatively greater distance of these cells from the source of supply. It will assist in the understanding of the structure and morphological characteristics of the several layers of cells to think of the superficial squamous cells in terms of the innermost columnar cells, modified during the passage to the surface by mechanical (pressure), physical (desiccation), and chemical (keratization) factors.

Pseudostratified Columnar Epithelium.—The superficial cells only of this variety of epithelium are columnar in shape, and except in one or two unimportant places are always ciliated. The deeper extremities of these columnar cells taper to a point, and extend all the way to the basement membrane. Between the tapering ends of these cells
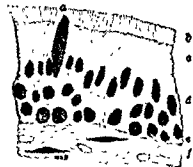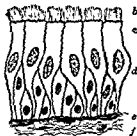

FIG. 57. — DIAGRAM SHOWING THE MANNER IN WHICH ALL THE EPITHELIAL CELLS OF PSEUDOSTRATIFIED CILIATED EPITHELIUM REACH THE BASEMENT MEMBRANE.

Letters as in the preceding figure.

small spindle-shaped spheroidal cells are closely packed. The several varieties of cells thus appear to be super-imposed, though all actually rest upon the basement membrane. The superficial cells of this variety extend throughout the entire thickness of the membrane. Hence this form of epithelium may in one sense be called simple rather than stratified. The distribution of this variety of the epithelium is practically identical with that of ciliated cells. The deeper extremities of the columnar cells are occasionally bifid or even somewhat varicose in order the more closely to fit between the spindle-shaped and spheroidal cells of the deeper portion. The nucleus of these latter cells is usually situated a little below the middle of the columnar cell, so that all the nuclei of the epithelial membrane lie within its deeper half, thus giving to this portion a more deeply chromatic appearance when observed in stained sections under low magnification. The superficial half of the epithelial layer contains only the cytoplasmic portion of the columnar cells with their ciliated borders.
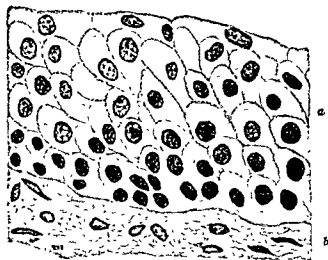

Fig 58—Transitional Epithelium from a Transection of the Ureter of an Infant. a, epithelium; b, connective tissue. Hematein and eosin. ×550.

This type of epithelium is frequently designated simply "stratified columnar," and in fact in certain instances under conditions of further modification involving a separation of the taller cells from the basement membrane, it passes, over more or less extensive areas in the respiratory and male genital tracts, into actual stratified columnar epithelium. Toward the proximal end of the male urethra the epithelium is of the true stratified columnar (nonciliated) type.

Transitional Epithelium.—This variety resembles somewhat stratified squamous epithelium in that it is composed of several cell layers, the deeper cells of which are more nearly polyhedral but are somewhat flattened upon the free surface, but differs in having a smaller number of cell layers—in which respect it is transitional between simple and stratified squamous epithelium—and in the character of the superficial cells. Transitional epithelium is not usually more than from three to ten cells deep, four to six being the rule. The number of cell layers and

the consequent actual thickness of epithelial membranes is to a certain extent dependent upon their state of tension during life; thus the transitional epithelium of the urinary bladder is much thicker when the organ is collapsed than during distension.

The deepest cells are polyhedral, and these form the greater portion of the membrane. Only the more superficial layers differ therefrom. Those polyhedral cells which lie in the midregion of the epithelial layer possess a peculiar flask or pear shape, with well-rounded bodies and a broad tapering process which is embedded between the adjacent cells of the deeper layers. The rounded extremities of the pear-shaped cells fit into peculiar indentations in the deeper surface of the superficial layer of epithelial cells, producing peculiar concave facets, which are specially characteristic of the detached superficial cells of transitional epithelium.
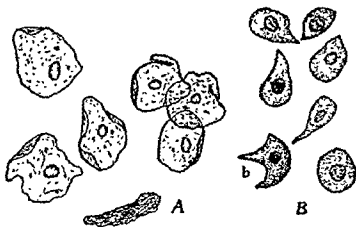

FIG 59.—ISOLATED CELLS WHICH MAY APPEAR IN HUMAN URINE.

A, from the vagina of a woman (stratified squamous epithelium); B, from the ureter of a child (transitional epithelium); a, cells from the deep layers; b, superficial cell. Moderately magnified

The superficial cells, while somewhat flattened, usually have a thickness equal to one-sixth to one-third their transverse diameter. In this respect they differ markedly from the superficial scaly cells of stratified squamous epithelium and are easily distinguished therefrom, even in the isolated condition in which they are frequently found in the urine. The concave facets on their under surface, as well as the peculiar pyriform shape and small size of the deeper cells, are sufficient to distinguish the transitional cells from those of stratified epithelium.

There is little, if any, formation of keratin in transitional epithelium. This is possibly explained by the fact that, as it occurs only in the urinary system, this form of epithelium is always well moistened. Differentiation of this variety of epithelial tissue, though neglected by some authors, becomes most important in the clinical examination of urine where it is necessary to determine the origin of individual cells. Transitional cells from the bladder are easily distinguished from the stratified squamous cells of the vagina, urethra, or epidermis.

CHAPTER III

CONNECTIVE TISSUE, CARTILAGE AND BONE

CONNECTIVE TISSUE

While in the epithelial tissues the cells are developed chiefly at the expense of the intercellular elements, in the connective or supporting tissues the conditions are the reverse. The intercellular elements are here developed out of all proportion to the connective tissue cells. The cells of these tissues therefore are scanty, the ground substance considerable, and within the latter a new element, the connective tissue fiber, makes its appearance. The fibers are of three varieties: *white or collagenous fibers, elastic fibers,* and *reticulum.* In any given location either of

FIG. 60.—EMBRYONAL CONNECTIVE
TISSUE, EARLY STAGE.
Highly magnified (After Mall)

FIG. 61.—EMBRYONAL CONNECTIVE TIS-
SUE AT A LATER STAGE THAN IS REP-
RESENTED IN FIGURE 60. (Mall.)

these varieties may predominate to such an extent as to determine the character of the mature tissue, while in the immature forms of connective tissue it is the cellular elements which attain the greatest prominence.

The minute structure of connective tissue is subject to great and important changes during its development. Beginning as it does with the primitive mesoderm, connective tissue is originally a cellular structure. The cells of primitive connective tissue, the *fibroblasts,* not only increase in number by cell division but also secrete an intercellular ground substance of semifluid consistence. The fibroblasts fuse with each other and finally form a syncytial tissue, the *mesenchyma,* in which there promptly occurs a differentiation of the cytoplasm with the formation of an endoplasm and an exoplasm; and within the latter the fine fibrils soon make their appearance, by alignment, subsequent fusion and chemical alteration of granules which may be designated as *fibrochondria.* Meves regards these initial granules as mitochondria (chondrioconts). The exoplasmic portion of the fibroblasts subse-

47

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dependent upon their state of tension during life; thus the transitional epithelium
of the urinary bladder is much thicker when the organ is collapsed than during
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Moderately magnified.

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individual cells. Transitional cells from the bladder are easily distinguished from
the stratified squamous cells of the vagina, urethra, or epidermis.

gradual consolidation and fusion of minute structural elements in a gelatinous, transparent cell-free ground substance. This ground substance pervades the embryonic body from very early stages of development and represents a secretion product of the cells of the several germ layers. Fibers, presumably fibrin fibrils,

make their appearance as a delicate net-like structure, in which it is claimed arise the long coarser fibers typical of connective tissues. Both chemical and mechanical factors are assumed to operate in the process. Harrison[2] supports this concept of intercellular fibrillogenesis in connective tissues on the basis of his study of the balancer membrane in salamander embryos. Maximow[3] records similar findings with regard to reticulum and collagen fibrils in tissue cultures of the thymus of rabbit and guinea-pig. The fibrils in these tissue cultures are described as arising apart from exoplasm, as extracellular formations and without relation to mitochondria or fibrin. He interprets his preparations as demonstrating also the transformation of initial reticulum fibrils into collagen fibrils.

The claim that the initial connective tissue fibrils arise in the extracellular tissue juice, in the manner of a coagulation process, is contradicted by the fact that dissociation of primary connective tissue with caustic potash, as in the case of the umbilical cord of pig embryos,[4] yields no free fibrils. Such dissociation frees

FIG. 63 —GROUP OF FIBROBLASTS FROM UMBILICAL CORD OF 10 MM. PIG EMBRYO, PARTIALLY DISSOCIATED WITH CAUSTIC POTASH.

This shows the extensively branching character of the cells, and the origin of the initial fibrils in exoplasm. The ultimate cell processes represent a fibril with a delicate sheath of cytoplasm. Fibrillogenesis in this type of connective tissue is an intracellular process. ×800.

only extensively branched cells with fibrils in the exoplasmic regions and throughout the finer cell processes (Fig. 63). These fibrils are argyrophil and react positively to Mallory's technic for reticulum. The finer fibrils are chemically different from the tonofibrils of certain epithelial cells. Certain coarser peripheral fibers resemble so-called fibroglia but their staining reactions and the fact that they split terminally into finer typical reticulum fibrils marks them as simply a coarser variety

[2] Harrison, 1925.
[3] Maximow, 1929.
[4] Jordan, 1939.

quently separates from the cells, and as it dissolves into ground substance it deposits its fibrils into the enlarging intercellular spaces. This process continues, new ground substance and fibers being constantly formed at the expense of the endoplasm until finally the remnant of the latter again forms isolated cells. The culmination of these changes results in the mature fibrillar connective tissue in which the cells are shrunken and scarce, though still capable of assuming renewed activity on demand of altered conditions. In the subcutaneous tissue many of these
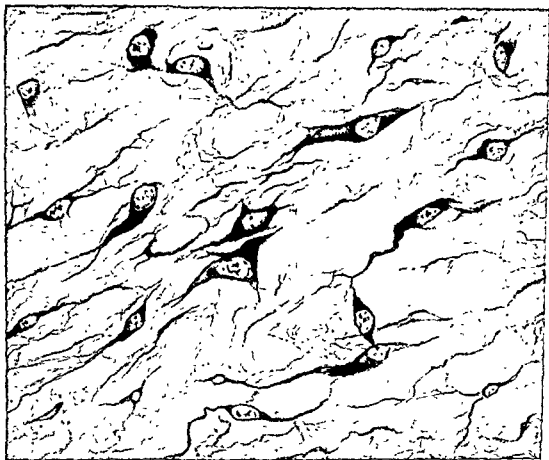

FIG. 62—AREA OF UMBILICAL CORD OF 10 MM. PIG EMBRYO.

The origin of initial connective fibrils in the protoplasm of the cell processes is shown. ×800 Foot's reticulum technic

small fibrocytes grow to original size and persist as potential fibroblasts. The definitive fibrils result in part from *longitudinal splitting of the coarser primitive fibers*, collagenous, elastic and reticular, both within the exoplasm of the fibroblasts and in later stages in the intercellular spaces.

Certain investigators describe a very different mode of fibrillogenesis. The process is said to be fundamentally intercellular rather than intracellular. In frog and chick embryos Baitsell[1] describes the origin of *connective tissue fibers* as a

_____
[1] Baitsell, 1915, 1925.

other methods of dissociation, yet on careful examination indications of fibrillar structure can be seen in the reticulum of fresh tissue and in ordinary microscopical preparations. The chemical reactions of the reticular fibers are similar to those of collagenous fibers except that the former are much less readily digested by artificial gastric juice.

Flattened connective tissue cells clasp the bundles of reticular fibers; they are mostly found at the intersections of the anastomosing bundles. This fact was accountable for the former theory, which regarded reticular tissue as formed by the anastomosing branches of stellate cells. The careful investigations of Carlier [10] and others have shown the true nature of the lamellar cells and their underlying fiber bundles.

The fibers of reticular tissue very closely resemble the collagenous fibers of areolar tissue, but differ from them in having a clearer, more highly refractive appearance. Their digestion in pepsin begins only after an interval of two hours, while white fibers are digested in a few minutes; they also stain less readily than white fibers and yield *reticulin*, which differs somewhat from the gelatin of white fibrous tissue. The intimate histologic relation between the reticular and white fibrous tissue is shown by the fact that the two tissues are frequently continuous and exhibit similar staining reactions.

Mall [11] has attempted to show that reticular tissue should be considered as that form of connective tissue which has been least differentiated from the embryonic mesenchymal type. He accordingly considers the cells of the recticulum as formed by the undifferentiated endoplasm, and the reticular fibers as representing the specialized exoplasm of this most primitive type of true connective tissue. In the liver, the reticulum arises from the endothelial cells of von Kupffer instead of directly from mesenchyma

Loose Fibro-elastic or Areolar Connective Tissue.—Loose fibro-elastic or areolar connective tissue (Fig. 64) is the most widely distributed of all the varieties; it fills all other unoccupied spaces within the body, and in all microscopical sections areolar tissue is almost invariably to be found. It is also known as *loose* connective tissue in contradistinction to the more compact or *dense* varieties. This tissue connects the skin with the underlying structures, maintains the position and relation of adjoining muscles, surrounds the heart and its great vessels, envelops the abdominal viscera as submucous and subserous sheets, occupies the spaces of the mediastinum, and fills similar intervals between the various organs

FIG 70—BUNDLE OF COLLAGEN FIBRILS AFTER TREATMENT WITH DILUTE ACETIC ACID

The white fibers swell and assume a beaded appearance The constrictions result from the presence of circular elastic fibers. The material is from the subcutaneous tissue of an albino rat. ×160.

[10] Carlier, 1895.
[11] Mall, 1902

of connective tissue fiber. The idea that the initial alleged intercellular fibers arise from fibrin fibrils produced by coagulation of the intercellular fluid under the influence of an enzyme liberated by the fibroblasts, is based upon the reaction of fibrin to Mallory's connective tissue stain. But the fact that fibrin and reticulum both stain blue by this technic cannot properly be regarded as proof of chemical identity or genetic relationship.

Embryonic connective tissue is typically cellular as compared with the mature type; its ground substance is abundant but the fibers, whose development is as yet incomplete, are scanty. Such embryonic connective tissue is found not only in the
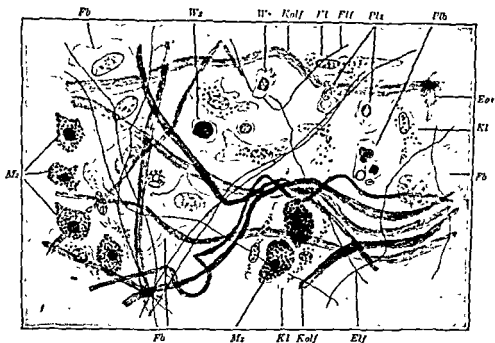
FIG. 64.—SUBCUTANEOUS AREOLAR CONNECTIVE TISSUE OF GUINEA-PIG (Maximow.)

Elf, elastic fiber; *Kolf,* collagenous (white) fiber bundles; *Fb* fibroblast (lamellar cell); *Mz,* mast cell; *Wz,* resting wandering cell (clasmatocyte); *Plz,* plasma cell; *Kl,* clasmatocyte (macrophage); *Eos,* eosinophil. ×1750.

fetus but also in early childhood and in the adult, especially during regeneration of destroyed areas of connective tissue, and in other more or less pathological conditions.

Connective Tissue Cells.—The cells of connective tissue include the following varieties: fibroblasts, phagocytes, mast cells, and plasma cells. The fibroblasts are subdivided on the basis of a difference in shape into: lamellar cells, stellate cells, and spindle cells. This order of division parallels in general an increase in differentiation (age) and a decrease in size of the fibroblasts.

The *phagocytes* of connective tissue are identical with the *monocytes* of the blood, and have an identical derivation, namely, from lymphocytes chiefly, and in part from reticulo-endothelium and young fibroblasts, particularly reticular cells. These phagocytes are commonly known as clasmatocytes, but are also referred to

quently branch and anastomose, forming in this way a very fine net with wide
meshes, within which are the interlacing bundles of white fibers. The elastic fibers
exist under a certain tension during life, so that their course under favorable con-
ditions is invariably straight. When areolar tissue is removed from the body this
tension is frequently relieved and the elastic fibers then curl up, especially at their
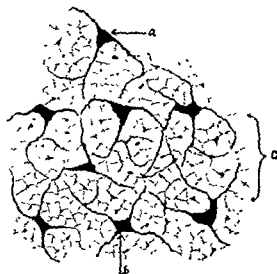free ends. Under these conditions they are no longer straight, but present a grace-

FIG. 73—TRANSVERSE SECTION OF PORTION OF TENDON OF HUMAN FINGER.

a, three-winged cell; *b*, four-winged cell; *c*, primary bundle, completely ensheathed by
the wings of tendon cells, and divisible into still smaller bundles of collagenous fibers out-
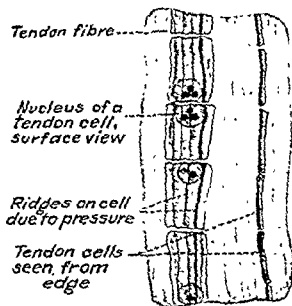lined by finer processes of the wings. The individual fibers are not shown. Gold chloride. ×1000.

FIG 74—PIECE OF TENDON FROM TAIL OF WHITE MOUSE.

Between the bundles of connective tissue-tissue fibrils are cells arranged in rows. Some
are seen in surface view, and others in optical section. ×400. (From Szymonowicz-
MacCallum, *Histology and Microscopic Anatomy*.)

fully curved contour. The elastic fibers also possess a glassy, shiny, or highly
refractive appearance, the collagenous fibers by comparison to them looking dull
and opaque.

Elastic fibers stain but slightly with most dyes; they are readily colored by
orcein and by Weigert's elastic tissue stain (resorcin-fuchsin), both of which serve
as specific dyes for these fibers, coloring the fibers dark brown or black. Elastic
fibers are not dissolved by dilute acids or alkalis even when boiled, and are only
digested by artificial gastric juice after a lapse of several hours; they are, however,
readily digested in faintly alkaline solutions of pancreatin. They consist of the
albuminoid body, *elastin*, which on boiling does not yield gelatin. Both collagenous
and elastic fibers arise by a similar process involving transformation of the exo-
plasm of their respective fibroblast progenitors. Whether the fibers are deposited

in all parts of the body. Areolar tissue of course varies in the degree of its laxity or density.

The *ground substance* of areolar tissue is a coagulable fluid, the *tissue juice*. Solutions of silver nitrate injected into the interstices of areolar tissue coagulate its tissue juice or ground substance and darken it slightly. It is then seen to be permeated by broad lymphatic channels, which are lined by delicate endothelioid mesenchymal cells.[12]
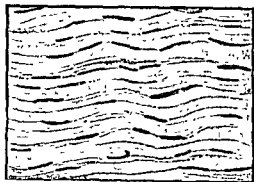
Both collagenous and elastic fibers occur in areolar tissue, the former being far in excess of the latter. The comparatively loose reticular arrangement of the fibers of fibro-elastic tissue affords a most favorable opportunity for the study of these connective tissue elements.

FIG. 71. — LONGITUDINAL SECTION OF TENDON OF HUMAN FINGER.

Only the nuclei of the tendon cells are conspicuous, scattered in rows among the collagenous fibrils. The rows of nuclei mark the boundaries of the primary bundles. ×750.

The *collagenous* or *white fibers* in mature tissues are invariably arranged in bundles which interlace with one another to form an open network. Each bundle consists of a number of very fine fibers whose course is characteristically wavy or undulating. Though the individual fibers rarely branch, the fiber bundles frequently anastomose with one another. The white fibers are readily stained with most acid dyes, and possess a special affinity for acid fuchsin. Chemically they consist of the albuminoid *collagen*, a "colla" or glue-producing substance, which on boiling in water yields gelatin, and is readily dissolved by boiling in dilute acids or alkalis Collagen fibers are digested by artificial gastric juice in five or ten minutes but are scarcely altered after several hours when acted upon by solutions of pancreatin or trypsin. After boiling, however, white fibers are readily digested by pancreatin. In dilute acids they swell and become transparent.
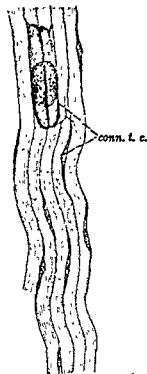

FIG. 72. — PORTION OF TENDON FROM A COW.

conn. t. c., connective tissue cells (tendon cells) seen from the side and, in one case, from the surface. (From Dahlgren and Kepner, *Animal Histology,* Macmillan Co.)

The *elastic fibers* of areolar tissue, in comparison with the collagenous fibers, are few in number. They occur as isolated fibers—never in bundles—which fre-

12 MacCallum, W. G, 1903.

Elastic fibers in this tissue are relatively few in number and are so obscured by the dense bundles of white fibers as to be scarcely demonstrable except by means of the specific stains. Tendon will be further discussed in connection with striped muscle.

Dense Elastic Tissue.—In this form of tissue the elastic fibers are developed at the expense of the collagenous fibers. The ground substance is insignificant in amount, and the connective tissue cells are scanty and are confined to the white fibrous sheaths in which the elastic fibers are enveloped. The elastic fibers are of very large size (10 to 15 μ) as compared with those of other forms of connective tissue. But except for their larger size, these fibers have the same peculiar characteristics as the elastic fibers of areolar tissue. In their straight course, frequent branches, and their glistening, highly refractive appearance, as also in their characteristic reactions to specific dyes and other reagents, these fibers are identical with the elastic fibers of the other types of connective tissue.

Fig. 77.—Transection of a Fasciculus of the Ligamentum Nuchae of the Ox, Showing the Very Large Elastic Fibers Embedded in a Very Delicate Network of Collagenous Fibers ×550.

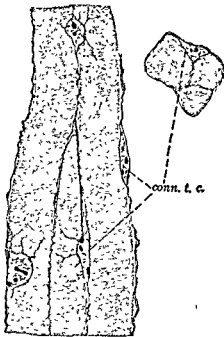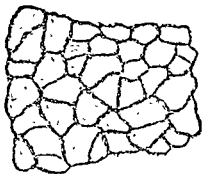The elastic fibers are bound together by delicate sheaths of very fine collagenous fibers, and are united into bundles by coarser bands of fibrous tissue. Elastic tissue is found in the ligamenta flava, the stylohyoid ligament, and in the ligamentum nuchae, which is especially highly developed in the neck of quadrupeds and commonly known as "whitleather." In these locations it occurs in considerable quantity and has a peculiar yellowish color; it is for this reason that it is frequently described as *yellow* elastic tissue. It occurs also as fenestrated membranes in arteries. These are formed by a coalescence of neighboring fibers. In the process of occlusion of the postfetal ductus arteriosus of the pig by increase in the amount of the elastic tissue in the wall of the artery, the new elastic fibers arise both from latent fibroblasts and by delamination of fibers from preformed elastic tissue.[13]

Fig 78—Portion of Ligamentum Nuchae of Ox.

conn t. c, connective tissue cells. (From Dahlgren and Kepner.)

Adipose Tissue (Fat Tissue).—Wherever areolar tissue occurs, adipose tissue may also be found; its distribution is therefore identical with that of areolar tissue. It forms a considerable mass, *panniculus adiposus*, beneath the skin of many parts. In it are embedded the kidneys,

[13] Schaeffer, 1914.

as such or arise by coalescence of more fundamental granular elements is a disputed point.
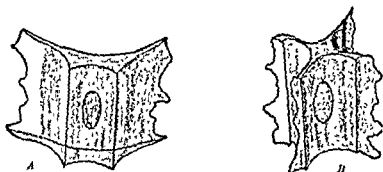

FIG. 75.—ISOLATED TENDON CELLS.

A, with two wings; *B*, with four wings. (From Maximow, after Tourneau.) ×1000

The *cells* of areolar tissue are few in number, but may include any of the several varieties, though lamellar and spindle cells together with leukocytes form the more common types. Many of the lamellar cells are closely applied to, or even wrapped around the bundles of white fibers. Fat cells occur in considerable numbers in all areolar tissue and in some places are aggregated into large groups which form lobules of fatty tissue.
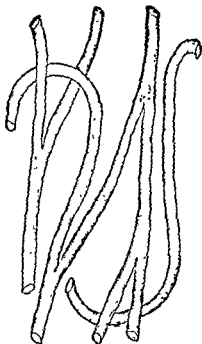
Dense Fibrous Tissue.—In dense fibrous tissue the ground substance is comparatively deficient. Large bundles of collagenous fibers are arranged in approximately parallel rows, and are so closely packed as to form a dense, firm, highly resistant tissue. Its scanty connective tissue cells are of the lamellar variety and are usually arranged in rows which occupy the interstices between the parallel fiber bundles.

FIG 76.—COARSE ELASTIC FIBERS FROM THE LIGAMENTUM NUCHAE OF THE OX

Isolated by teasing Partly diagrammatic. × about 250

Dense fibrous tissue occurs typically in tendons; in these the connective tissue cells often have a peculiar quadrate shape and are arranged in rows of exceptional regularity (Figs. 71-74). These should be studied in dissociated tendinous tissue. It also forms the ligaments, the fasciae, the muscular sheaths (aponeuroses), and the enveloping capsules of many of the viscera. Thus it surrounds the liver, kidney, lymph nodes, and other organs; it also forms the valves of the heart, the tendinous rings which surround the cardiac orifices, and the chordae tendineae which are attached to its valves; and in general, it may be stated that dense fibrous tissue is found wherever great firmness and resistance are required.

involving the use of alcohol or ether, since these reagents extract fat from the cells. Fat, in cooling, solidifies and precipitates delicate threads, the *margarin crystals*.

Fat as ordinarily found in the body is a mixture of true fats and fat-like substances or lipoids True or neutral fats, the triglycerides of oleic, palmitic and stearic acids, are isotropic; lipoids, *e g.*, lecithin, myelin and cholesterin, are anisotropic in physical character. As commonly used in histology lipoids include fats, fatty acids, phosphatides, cholesterol, etc., that is, substances which have the same solvents and which are found associated in cytoplasm.

During periods of starvation or malnutrition, at which time fat decreases greatly in volume, many of the fat cells return to a condition which approximates their former state. As the fat is removed the cytoplasm of the cell increases in amount, but assumes a peculiar fluid appearance and is not readily colored by the usual dyes These cells, which still contain a number of fat droplets, are known as "serous" fat cells.

Recent investigations have explained the earlier disagreements regarding fat histogenesis. It is now known that in many species of mammals there occur definite regions in which fat develops from sharply circumscribed, lobulated masses of peculiar ovoid, granular cells very different from the usual lipoblast. This adipose tissue has been variously described as "brown fat," "adipose gland," "hibernating gland," "interscapular gland" and "cholesterin gland." The most definite mass occurs between the dorsal borders of the scapulae, hence the name "interscapular gland." This type of adipose tissue changes in man during infancy into a tissue indistinguishable from the fat which develops directly from connective tissue. According to Bonnot [14] remnants may persist in the adult. This tissue has been designated as the "gland of Bonnot." King [15] describes fairly constant masses of brown fat in man on the posterior aspect of the interior abdominal wall and in the retroperitoneal tissue in the iliac region. In the white rat, tame mouse, and hibernating animals such fat maintains throughout normal life its specific embryonal appearance Cramer [16] regards this glandular type of adipose tissue as functionally closely related to the endocrine glands, especially the thyroid and suprarenal.

The forerunners of the original smallest fat droplets are granules (Altmann, 1890). In the subcutaneous tissue of Myxine (hagfish) embryos, Schreiner [17] has
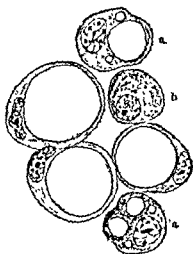
FIG. 80.—A GROUP OF FAT CELLS FROM THE SUBCUTANEOUS TISSUE OF A YOUNG RABBIT.

Cells *a* show stages in development; cell *b* is cut tangentially through the nucleated pole. ×1000.

[14] Bonnot, 1908.
[15] King, 1931
[16] Cramer, 1920.
[17] Schreiner, 1915.

suprarenals, and many lymphatic nodes. The mesentery and omentum are freely supplied with fat. The same tissue is found in the grooves of the heart wall and it also occupies the spaces of the mediastinum.

Adipose tissue is composed of *lobules* or groups of fat cells which are supported by fibrous bands and septa and are abundantly supplied with small blood vessels.

The fat cells arise from the connective tissue cells by a deposit of fat droplets within the cytoplasm of the latter. Such cells constitute *lipoblasts*. The fat droplets continue to increase in number and fuse with each other to form globules of
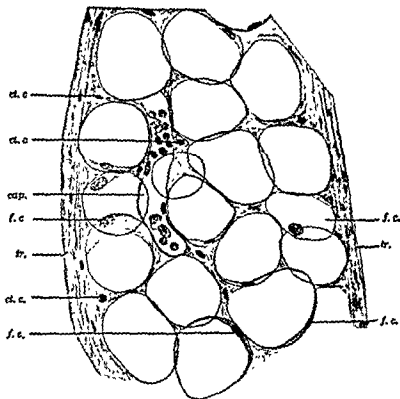

FIG. 79.—PORTION OF A FAT LOBULE FROM THE AREOLAR CONNECTIVE TISSUE SURROUNDING THE ESOPHAGUS OF A CAT.

cap., capillary; *ct. c*, nucleus of a connective tissue cell; *f c.*, fat cell showing nucleus; *tr*, trabecula of fibro-elastic connective tissue. ×500.

increasing size, until the cytoplasm finally becomes so excavated as to form a mere limiting membrane or cell wall (Fig. 80). The nucleus is pushed to one side in this process and is flattened against the cell membrane; it is usually embedded in a remnant of granular cytoplasm. Being thus distended with fluid fat, the cell acquires a spheroidal shape.

The routine specific stains for fat are osmic acid, which colors the fat globules black; sudan III, which gives a red reaction; and scharlach R (fettponceau, sudan IV), which also stains fat red. For the successful application of these stains it is required that the tissue has not been previously subjected to treatment

Lymphoid Tissue (Adenoid Tissue).—Lymphoid tissue is a reticular tissue the meshes of whose network are occupied by a closely packed mass of lymphocytes, cells with a deeply staining nucleus enveloped by a narrow shell of homogeneous slightly basophilic cytoplasm. The lymph cells (lymphocytes) are so closely
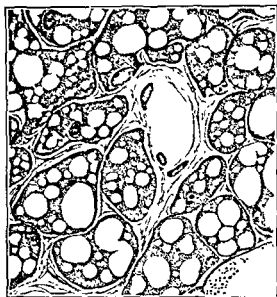

FIG. 83—COLLECTION OF DEVELOPING FAT CELLS FROM THE "PERIRENAL LIPOID GLAND" OF THE MOUSE.

The irregularly ovoid cells contain granules and vacuoles, interpreted as mitochondria and lipoid globules respectively. ×1400. (Cramer.)

FIG 84.—RETICULUM FROM THE MUCOSA OF THE FUNDUS REGION OF THE DOG'S STOMACH.

The section was made parallel to the surface and the glandular tissue removed by shaking in water. ×125. (Mall.)

described the process of fat elaboration in minute detail. The pre-fat granules originated from rod-like chromidia (mitochondria) by process of segmentation. The chromidia arise as nucleolar buds which wander through the nucleus and traverse the nuclear membrane as spherical granules. These primary granules
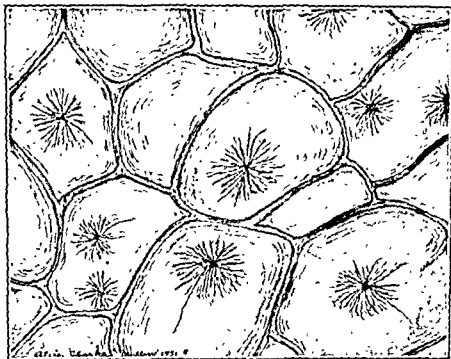

FIG. 81.—COLLECTION OF FAT CELLS SHOWING MARGARIN CRYSTALS.
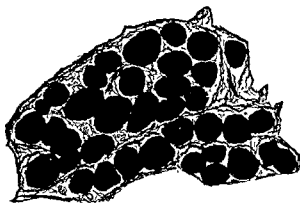Two of the cells show two centers of crystallization each. Fresh preparation. Unstained.

FIG. 82.—ADIPOSE TISSUE.
The fat cells have been blackened by osmium tetroxide ×110.

elongate into rods, and subsequently segment into secondary granules, which liquefy and coalesce to form the definitive fat spherules. This important investigation suggests a functional rôle for mitochondria in terms of a nutritive material upon which cell metabolism and differentiation may depend.

purpose consists in injecting gelatin into a fresh lymph organ (*e.g.*, spleen), freezing the tissue, and placing thin sections into warm water when the lymphocytes are largely carried away by the dissolving gelatin leaving the reticulum free.

The density of the lymphoid tissue varies much in different organs and even in different portions of the same organ. The denser accumulations of lymphoid corpuscles may form either ovoid *lymph nodules* or *follicles*, or long dense trabeculae, the *lymphatic cords*, which are surrounded by looser portions of lymphoid tissue.

Lymphatic corpuscles are frequently infiltrated into the connective tissue of the mucous membranes, where they form irregular collections, which may be termed *diffuse lymphoid tissue*, in contradistinction to *compact lymphoid tissue*, which occurs in the lymph nodes, tonsils, thymus and spleen, and in the aggregate and solitary nodules of the intestinal canal. Diffuse lymphoid tissue is found in the mucous membranes of the *respiratory tract—nose, nasopharynx, larynx, trachea, and bronchi;* and the alimentary tract—mouth, tongue, pharynx, esophagus, stomach, and intestines.

In the basement membranes of certain tubular glands—*e.g.*, sweat, kidney, tear and mammary—and in the peripheral portion of the large cells of the umbilical cord, Mallory [18] has described robust fibers extending also from cell to cell, resembling somewhat white fibers, but unrelated by transition elements to, and differing micro-

Fig 87.—From a Section through the Medulla of a Cervical Lymph Node of Man.

a, a cord of dense lymphoid tissue; *b*, looser lymphoid tissue of the medullary sinuses; *c*, the margin of a fibrous trabecula; *d*, nucleus of the connective tissue reticulum; *e*, reticulo-endothelial lining of the lymphatic sinus. ×475.

chemically from, collagenous fibers. These so-called *fibroglia fibrils* (*tonofibrils*) are said to be similar to the fibrils of neuroglia cells of nervous tissue and to the border or myogha fibrils of plain muscle cells.

Blood and Nerve Supply of the Connective Tissues.—The connective tissues, but *especially the areolar variety*, form a supporting substance through which the various blood and lymphatic vessels and nerve trunks are distributed to all portions of the body. Within the connective tissues these vessels and nerves are everywhere present, and from them the connective tissue itself receives its supply of capillary vessels and terminal nerve fibrils.

The vascular supply of the connective tissues is abundant. Small arteries, which
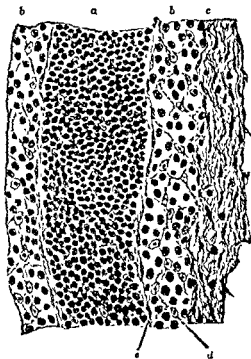
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[18] Mallory, 1905

packed that it is almost impossible to distinguish the fine threads of the reticular stroma, except in those portions where some of the lymphatic cells have been washed out or displaced in the preparation of the specimen. Mall's technic for this
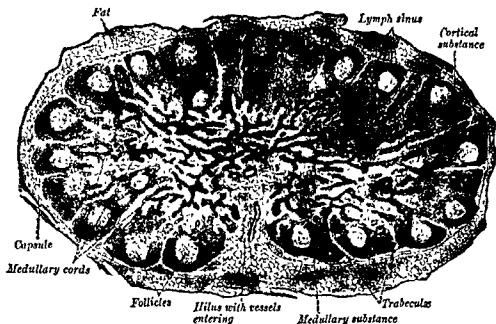

FIG. 85—SECTION THROUGH A SMALL LYMPH NODE OF A DOG.
×20. (From Szymonowicz-MacCallum, *Histology and Microscopic Anatomy.*)

FIG 86—STROMA OF LYMPHOID TISSUE FROM LYMPH GLAND OF CAT.

The net-forming fibers are sheathed by a protoplasmic syncytium with nuclei The lymphocytes in the meshes are not shown (M. Heidenhain)

purpose consists in injecting gelatin into a fresh lymph organ (*e.g.*, spleen), freezing the tissue, and placing thin sections into warm water when the lymphocytes are largely carried away by the dissolving gelatin leaving the reticulum free.

The density of the lymphoid tissue varies much in different organs and even in different portions of the same organ. The denser accumulations of lymphoid corpuscles may form either ovoid *lymph nodules* or *follicles*, or long dense trabeculae, the *lymphatic cords*, which are surrounded by looser portions of lymphoid tissue.

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In the basement membranes of certain tubular glands—*e.g.*, sweat, kidney, tear and mammary—and in the peripheral portion of the large cells of the umbilical cord, Mallory[18] has described robust fibers extending also from cell to cell, resembling somewhat white fibers, but unrelated by transition elements to, and differing microchemically from, collagenous fibers. These so-called *fibroglia fibrils* (*tonofibrils*) are said to be similar to the fibrils of neuroglia cells of nervous tissue and to the border or myogha fibrils of plain muscle cells.

FIG 87.—FROM A SECTION THROUGH THE MEDULLA OF A CERVICAL LYMPH NODE OF MAN.

a, a cord of dense lymphoid tissue; *b*, looser lymphoid tissue of the medullary sinuses; *c*, the margin of a fibrous trabecula; *d*, nucleus of the connective tissue reticulum; *e*, reticulo-endothelial lining of the lymphatic sinus. ×475.

Blood and Nerve Supply of the Connective Tissues.—The connective tissues, but especially the areolar variety, form a supporting substance through which the various blood and lymphatic vessels and nerve trunks are distributed to all portions of the body. Within the connective tissues these vessels and nerves are everywhere present, and from them the connective tissue itself receives its supply of capillary vessels and terminal nerve fibrils.

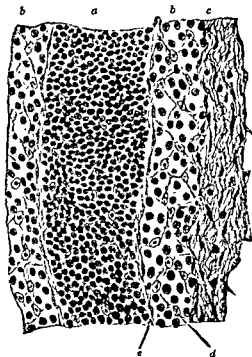The vascular supply of the connective tissues is abundant. Small arteries, which

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[18] Mallory, 1905.

are derived from the main trunks, form a capillary plexus throughout the tissue, the capillaries finally reuniting to form the venules.

It is in this capillary plexus that the fluid portions of the blood exude into the surrounding perivascular lymphatic or tissue spaces of the connective tissue. *The tissue juices which arise in this manner are most active agents in the physiological processes of assimilation.* From the tissue juice spaces, lymph reënters the abundant capillary lymphatic vessels to be finally returned to the venous blood. This
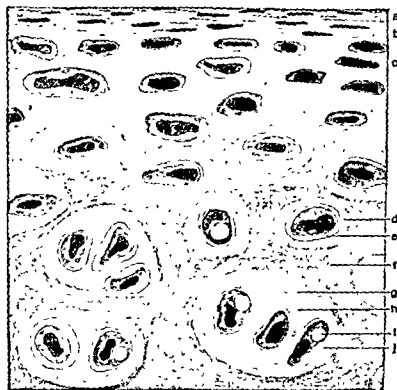

FIG 88.—SECTION OF PLATE OF HYALINE CARTILAGE, FROM TRACHEA OF CAT.

a, perichondrium, *b*, chondrogenetic layer of perichondrium; *c*, young hyaline matrix and cells, *d*, capsule, *e*, peripheral portion of the lacuna occupied by the cartilage cell; *f*, older hyaline matrix, *g*, capsule of the original mother cell; *h*, lacuna of the original mother cell, now filled with younger matrix produced by the three daughter cells; *i*, fat vacuole in the cytoplasm of a cell; *j*, capsule of one of the three daughter cells ×650

transfer is mediated by process of filtration and osmosis, the tissue spaces being generally regarded as closed spaces making no direct connection with the lymphatic terminals. Of the several varieties of connective tissue, the adipose possesses the most abundant blood supply; the lymphoid, on the other hand, is most richly supplied with lymph.

Abundant nerves are distributed to the connective tissues, some of which, the sympathetic nerves, supply its blood vessels while others, myelinated, terminate in special forms of sensory nerve end-organs.

CARTILAGE

Cartilage is a dense, firm, but elastic substance, resembling connective tissue in that it is developed from similar mesodermal cells. It contains a ground substance, the cartilage matrix, and at times, fibers which may be either collagenous or elastic. The presence, absence, or character of these fibers determines the variety of cartilage. Three varieties are thus distinguished: *hyaline cartilage*, in which no specific fibers can ordinarily be demonstrated within the matrix; *elastic cartilage*, whose matrix is permeated by elastic fibers; and *fibrocartilage*, whose matrix contains collagenous fibers.

Hyaline Cartilage.—This is the most abundant of the three varieties, commonly known as gristle. It is found in the respiratory system, forming the cartilages of the nose, larynx, trachea and bronchial tubes; in the costal cartilages of the ribs; as articular cartilages covering the ends of long bones; and in the fetus, where in the course of development of the bones, the entire skeleton, excepting only the flat bones of the skull and face, at first consists of hyaline cartilage. In most of these locations the cartilage occurs as plate-like masses, which are invested by a vascular membrane of dense fibro-elastic tissue. This membrane is the *perichondrium*. The inner portion of this membrane is richly supplied with small cells, and it is from this cell layer, the chondrogenetic layer, that the cartilage is presumably developed.

FIG. 89—CELLS AND MATRIX OF HYALINE CARTILAGE FROM THE WALL OF A LARGE BRONCHUS OF MAN.

The grouping in pairs and fours, and the tendency to produce a so-called capsule, are especially noticeable. Hematem. × 550.

The cartilage blastema is essentially mesenchyma. The chondrogenetic cells of this *precartilage* multiply, and deposit about themselves the structureless mass which at first forms merely a *capsule* to the cell, but which as it increases in amount, separates the various cells by wider areas and becomes the *cartilage matrix*. The process of matrix formation may be interpreted as a conversion of the exoplasm of the syncytial tissue, the cartilage cell representing the endoplasm. The so-called capsule of the cartilage cell would accordingly represent the partially modified border line between the original endo- and exoplasm, and would thus correspond to similar conditions which are observed in other forms of developing connective tissue

The cells, which in the perichondrium are small and decidedly flattened, likewise increase in size during this process, and become more nearly spherical, so that those *cartilage cells* (chondrocytes) which lie near the center of the cartilaginous

plates are spheroidal in shape, while those toward the surface are more and more flattened or elongated, their long axes gradually revolving from a perpendicular position in the center of the plate to one parallel with the perichondrium at the surface. Each cartilage cell is inclosed within a small space or *lacuna*, which during life it entirely fills.

Cell multiplication in cartilage is peculiar in that cell division occurs within a firm capsule and results in the formation of two daughter cells, which at first lie within the same encapsuled space. These two cells may each again undergo division within the same space with formation of four new cells. As a result of this peculiar method of cell division the cartilage cells are arranged in groups of two, four, or even eight cells. Each of the cells in the group deposits its capsule, and thus forms a matrix about itself, so that the increasing space thus produced between

the cells of a group may separate them until they become completely isolated cartilage cells each within its own *lacuna*. In this way the matrix of the cartilage is produced. Enlargement of a cartilage plate occurs through a combination of interstitial and perichondrial growth. The matrix of hyaline cartilage is devoid of fibrous or cellular structure. Chemically it consists of collagen, chondromucoid and albuminoid substances. Von Korff [19] interprets hyaline matrix as being composed of matrical fibrils masked by a homogeneous cementing substance.

During life, or if the tissue is examined in the fresh state, the cartilage cell entirely fills the lacuna in which it lies. But shortly after death shrinkage of these cells begins, so that after some hours a considerable space intervenes between the cell and the wall of its lacuna. It has been supposed
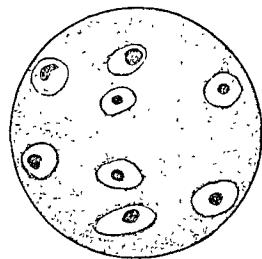

FIG. 90—ELASTIC CARTILAGE FROM THE HUMAN EPIGLOTTIS, SHOWING THE LARGE OVOID CARTILAGE CELLS AND THE VERY DELICATE RETICULUM OF ELASTIC FIBERS

Ehrlich's triacid stain. ×550.

that this space was occupied during life by lymph. It would, however, seem more probable that it is partially the result of postmortem shrinkage of the cell.

Frequently, and especially in developing cartilage, concentric lines may be seen surrounding each lacuna. These lines have been described as the "cell capsule." They appear only to indicate the successive layers of material which have been deposited by the cell, and which have been fused together to form its surrounding matrix.

Cartilage cells frequently contain small droplets of fat, and these may coalesce until the cell is completely transformed into a fat cell. Isolated masses of adipose tissue, resulting from the transformed groups of cartilage cells, thus make their

[19] von Korff, 1914.

appearance within the cartilaginous plates. This fatty metamorphosis is most marked in the elastic variety of cartilage.

By coloration with iodine, glycogen granules may also be demonstrated in the cartilage cells.

Elastic Cartilage.—Elastic cartilage occurs in the external ear, in the auditory tube, in the epiglottis and in the cuneiform and corniculate cartilages and the vocal processes of the arytenoid cartilages of the larynx. It is essentially hyaline cartilage, the matrix of which has become permeated with delicate elastic fibers forming a dense interlacing network. The large spheroidal cartilage cell lies in a lacuna bounded by a capsule and surrounded by a layer of hyaline matrix free of elastic fibers. The plates of elastic cartilage, like the hyaline variety, are surrounded by a dense fibrous perichondrium. Neither blood vessels, nerves, nor lymphatics are distributed within the matrix of elastic cartilage.

Fibrocartilage.—This tissue forms the interarticular cartilages of the lower jaw, the clavicle, and the knee; composes the intervertebral disks and the other cartilaginous symphyses of the body; lines the tendon grooves of the bones, and forms the glenoid ligament of the shoulder and the cotyloid ligament of the hip. Fibrocartilage is intermediate in structure between hyaline cartilage and such very dense fibrous tissue as occurs in the tendons of muscles. At the attached margins of the cartilaginous plates its tissue is continued by imperceptible gradations into the surrounding fibrous connective tissues. Like the other forms of cartilage, this variety is also nonvascular and devoid of nerves.

Microscopically, fibrocartilage differs from such dense white fibrous tissue as is found in the ligaments and tendons, in that the meshes of the dense fibrous tissue of fibrocartilage are everywhere permeated by a hyaline matrix in which here and there are small groups of ovoid cartilage cells. Each cartilage cell is occasionally surrounded by a characteristic, concentric, lamellar appearance of the adjacent matrix, the so-called capsule. Plates of fibrocartilage, unlike the other varieties, are not surrounded by a perichondrium.

A peculiar sort of connective tissue is found in the nuclei pulposi of the intervertebral disks. It is the sole adult vestige of the embryonic axis, the notochord. According to Williams,[20] who carefully studied its cytomorphosis in the pig, "It is primarily cellular and epithelial; later it becomes a syncytial network with a mucin-like substance in its vacuoles; and finally it becomes cellular and closely resembles cartilage."

The Perichondrium.—The perichondrium is a dense fibrous membrane which surrounds each individual plate of cartilage. It is continuous with the surrounding connective tissue, and is well supplied with blood vessels and lymphatics; it may also contain terminal nerve fibrils.

The cartilage itself is an absolutely bloodless and nerveless tissue. Neither are lymphatic channels demonstrable within the cartilage matrix. After long maceration or artificial digestion the matrix assumes a granular or fibrous appearance, and small channels have been demonstrated within it, which have been said to

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[20] Williams, L. W., 1908.

plates are spheroidal in shape, while those toward the surface are more and more flattened or elongated, their long axes gradually revolving from a perpendicular position in the center of the plate to one parallel with the perichondrium at the surface. Each cartilage cell is inclosed within a small space or *lacuna*, which during life it entirely fills.

Cell multiplication in cartilage is peculiar in that cell division occurs within a firm capsule and results in the formation of two daughter cells, which at first lie within the same encapsuled space. These two cells may each again undergo division within the same space with formation of four new cells. As a result of this peculiar method of cell division the cartilage cells are arranged in groups of two, four, or even eight cells. Each of the cells in the group deposits its capsule, and thus forms a matrix about itself, so that the increasing space thus produced between
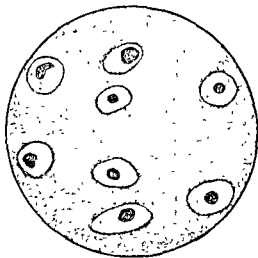

Fig 90—Elastic Cartilage from the Human Epiglottis, Showing the Large Ovoid Cartilage Cells and the Very Delicate Reticulum of Elastic Fibers

Ehrlich's triacid stain. ×550.

the cells of a group may separate them until they become completely isolated cartilage cells each within its own *lacuna*. In this way the matrix of the cartilage is produced. Enlargement of a cartilage plate occurs through a combination of interstitial and perichondrial growth. The matrix of hyaline cartilage is devoid of fibrous or cellular structure. Chemically it consists of collagen, chondromucoid and albuminoid substances. Von Korff [19] interprets hyaline matrix as being composed of matrical fibrils masked by a homogeneous cementing substance.

During life, or if the tissue is examined in the fresh state, the cartilage cell entirely fills the lacuna in which it lies. But shortly after death shrinkage of these cells begins, so that after some hours a considerable space intervenes between the cell and the wall of its lacuna. It has been supposed that this space was occupied during life by lymph. It would, however, seem more probable that it is partially the result of postmortem shrinkage of the cell.

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Cartilage cells frequently contain small droplets of fat, and these may coalesce until the cell is completely transformed into a fat cell. Isolated masses of adipose tissue, resulting from the transformed groups of cartilage cells, thus make their

spongy appearance as compared with the denser periphery; it is therefore said to contain *spongy* or *cancellous bone*, while the more superficial lamellae contain *compact bone.*

In the long bones a similar condition exists in the epiphyses, which consist of a wall of compact bone within which the marrow cavity is subdivided by bony partitions into numerous compartments. The epiphysis consists, therefore, of spongy bone. The shaft or diaphysis of the bone, however, contains a single large marrow cavity whose walls, except for a thin layer at either end, consist entirely of compact bone. A little spongy structure is present for some distance at either end of the shaft, in that portion which adjoins the marrow cavity.

The ends and facets of the bones are covered by a disk of hyaline cartilage, which forms the articulating surfaces of those bones which enter into the forma-
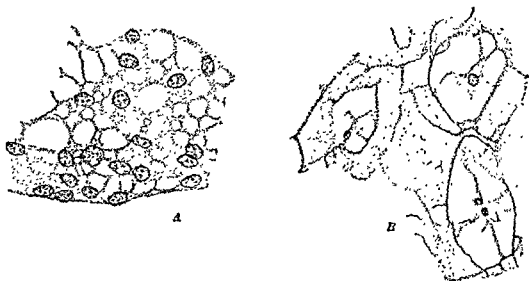
FIG 92.—NOTOCHORDAL TISSUE.

A, from pig embryo of 150 millimeters, the syncytium contains many mucin-filled spaces. ×800 *B*, from nucleus pulposus of an adult pig; the three cells shown are greatly vacuolated ×452. (Williams)

tion of the movable joints. These *articular cartilages* are peculiar in that they are not covered by a perichondrium, and their deeper cells, which adjoin the bone, are so arranged that their long axes are perpendicular to the free surface, as is the case in the central portion of free cartilaginous plates. Toward the free surface of the cartilage the long axis of the cell lies more nearly parallel to the surface, as is likewise the case at the surface of cartilaginous plates elsewhere. In the long bones of younger individuals a plate of hyaline cartilage is found also at the *epiphyseal lines* between the epiphysis and the diaphysis. This plate, which extends through the entire axis of the bone, becomes ossified later in life. It represents the line of longitudinal growth, and is the last portion of fetal cartilage to be transformed into adult bony tissue.

Periosteum.—All those portions of the bone which are not covered by an articular cartilage are supplied with a membranous coat of fibrous tissue, the

connect the various lacunae; but it is evident that these appearances were possibly the result of artificial destructive processes and could not therefore be considered as evidences of the presence of such structure in living cartilage.
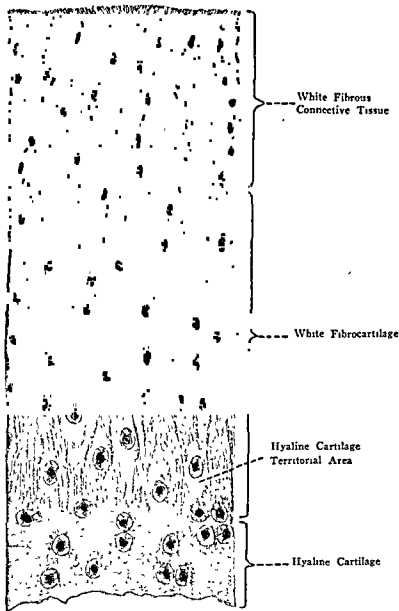

White Fibrous Connective Tissue

White Fibrocartilage

Hyaline Cartilage Territorial Area

Hyaline Cartilage

FIG. 91 —WHITE FIBROCARTILAGE FROM THE LIGAMENTUM TERES OF DOG. (Hardesty)

BONE

Bone is a firm calcareous tissue which is found only in the skeletal system. In the flat bones it forms a double layer of dense osseous tissue between which is a narrow space, bridged across at frequent intervals and thus subdivided into a number of compartments, the marrow cavities. This central stratum presents a

(0.05–0.1 millimeter in diameter), which is occupied by connective tissue, marrow cells derived from the marrow cavity during the process of development, small blood vessels, nerve fibers, and perivascular lymphatics. Concentrically arranged around the haversian canal are parallel layers of dense fibrous tissue, the *haversian lamellae*. The fiber bundles of this tissue form an interlacing network whose bundles frequently cross each other at right angles and whose interstices are occupied by a solid calcareous mass, consisting chiefly of the phosphates (about 80 per cent) and carbonates of calcium. From four to twenty such calcareous lamellae are found in each haversian system. The organic substance of bone consists chemically of collagen, osseomucoid and small amounts of other albuminoid bodies.

Both in and between the lamellae are many small ovoid spaces which are partially filled by small flattened cells, the *bone cells (osteocytes)*; these spaces are known as the *lacunae*. From each lacuna minute canals, the *canaliculi*, radiate in all directions, thus placing the lacuna in open communication with its neighbors, and eventually with the lymph spaces of the central haversian canal. The branching processes of the bone cells frequently project for a short distance into the canaliculi. These cytoplasmic branches are more numerous in newly formed bone, later they are retracted and the cells become more or less shriveled in appearance.

The haversian system, being developed about a central canal which marks the course of a blood vessel, necessarily acquires a slender columnar shape, its long axis being usually disposed in a direction nearly parallel to that of the bone of which it forms a part. The haversian canals frequently branch to permit a corresponding division of their blood vessels, and all of the haversian canals are connected either directly or indirectly with the periosteum, the nutrient foramina, or the marrow cavity—thus forming a complete connected system between marrow cavity and surface—from the blood vessels of which their vascular supply is derived.

FIG 94—LONGITUDINAL SECTION OF GROUND BONE FROM THE SHAFT OF THE HUMAN FEMUR.

a, Haversian canals; *b*, lacunae; *c*, canaliculi. ×100 (Kölliker)

Interstitial Lamellae—The interstitial lamellae are likewise composed of dense interlacing bundles of calcified fibrous tissue, within and between which are lacunae, canaliculi, and bone cells, all disposed in a manner exactly similar to their arrangement within the concentric lamellae of the haversian systems. Coursing through the interstitial and circumferential lamellae are *Volkmann's canals*, which are similar in origin, contents, and function to the haversian canals but which are
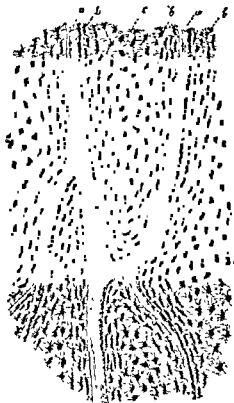
periosteum. The outermost layer of this membrane consists of interlacing bundles of dense fibrous tissue in which are the larger blood vessels, whose branches are distributed to the underlying bone. The inner portion of this layer forms a firm

FIG. 93.—TRANSECTION
THROUGH THE COMPACT
BONY WALL OF A HUMAN
METACARPAL BONE.

a, outer circumferential
lamellae; *b*, inner circum-
ferential lamellae; *c*, haver-
sian canals; *d*, interstitial
lamellae; *e*, lacunae, with
delicate radiating canaliculi.
From a thin section of
ground bone. × 90. (Kölli-
ker.)

fibro-elastic stratum, which in older individuals is closely attached to the surface of the bone. The periosteum of developing and growing bone, how-ever, contains a third or innermost areolar layer, in which are small blood vessels, fine connective tissue fibrils, and numerous small osteogenic cells, the *osteoblasts.* After growth of the bone has ceased, the deepest layer of the periosteum contains few small blood vessels and only occasional osteo-blasts. These cells, however, are present in sufficient numbers to accomplish the regeneration of the bone after destruction of its osseous tissue.

The medullary surface of the bone is likewise supplied with an osteogenic membrane of fibro-cellular tissue, similar to the innermost layer of the periosteum; it is known as the periosteum in-ternum, *endosteum,* or membrana medullaris.

Compact Bone.—Compact bone, such as that composing the shafts of the long bones, consists of *concentric lamellae* of calcified fibrous tissue which constitute the *haversian systems,* together with groups of parallel laminae, which are inter-posed between adjacent haversian systems and are known as the *interstitial* or *ground lamellae.* Many of the interstitial lamellae are the remains of haversian systems which have been partially ab-sorbed during the development of the bone. In a section through the shaft of a long bone the haversian systems are found in the middle of the wall, while superficial to them and just within the periosteum are a number of lamellae which may be traced much or all of the way around the cir-cumference of the cylindrical shaft, and which are known as the *external circumferential* or *periosteal lamellae.* On the inner surface of the compact bony wall is a similar group of parallel laminae which adjoin the marrow cavity, and are known as the
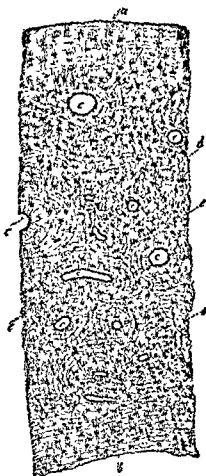
internal circumferential or *endosteal lamellae.* In their finer structure the circum-ferential lamellae are exactly similar to the cylindrical bony lamellae of the haversian systems

Haversian System.—An haversian system contains a small central canal

the relative proportion of these elements marrow is said to present two types, the *yellow* and the *red marrow*. The yellow marrow consists almost entirely of fat, with only occasional bands of true marrow tissue. The red marrow contains very little fat, but is so abundantly supplied with blood and marrow cells as to resemble closely a very vascular lymphoid tissue. The embryonic medulla of all bones contains fetal red marrow, but in later life the larger masses in the medulla of the shafts of the long bones are, in man, changed to the yellow variety. The red marrow, however, persists in the epiphyses of the long bones and in cancellous bone generally; it is especially characteristic of the marrow cavities of the ribs, vertebrae, base of the skull, and sternum. It is the source of supply of blood cells in the adult.

FIG. 96 — ISOLATED BONE CELL, SHRUNK AWAY FROM WALL OF LACUNA AT 1

(Schafer, after Joseph.)

Red Marrow.—Red marrow consists of fibrous and reticular tissues which are infiltrated by marrow cells and richly supplied with small blood vessels. The smaller veins possess exceedingly thin walls, readily pervious to the blood cells. The walls are so delicate that it becomes very difficult to determine with certainty whether or not their endothelium, as also that of the capillaries, may be occasionally absent, thus placing the blood stream in direct communication with the pulp of the bone marrow. This endothelium belongs to the type known as *reticulo-endothelium.*
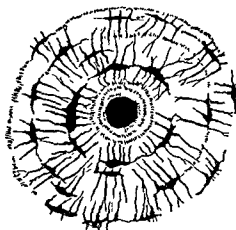

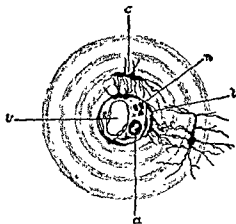FIG. 97 — AN HAVERSIAN SYSTEM, INCLUDING THE CENTRAL CANAL, SEVERAL LAMELLAE, LACUNAE AND CANALICULI

FIG 98 — TRANSVERSE SECTION OF HAVERSIAN CANAL, WITH CONTENTS

a, arteriole; *v*, venule; *l*, lymphatic; *n*, unmyelinated nerve fibers; *c*, bone cell. (Schafer.)

The hemogenic elements of marrow will be described under the subject of blood development, where red marrow must again be considered. At this point it is only necessary to describe the osteogenic elements. These are (1) the *osteoblasts,* or bone builders, and (2) the *osteoclasts,* or bone destroyers. The osteogenic process

not surrounded by concentric lamellae. Volkmann's canals frequently arise as branches of the haversian canals which wander out, as it were, into the interstitial lamellae.

Circumferential Lamellae.—The circumferential lamellae do not differ in structure from the other osseous lamellae. They possess the same arrangement of laminated calcareous connective tissue, with lacunae, canaliculi, and bone cells, as in the concentric and interstitial lamellae. Even more than elsewhere, however, the
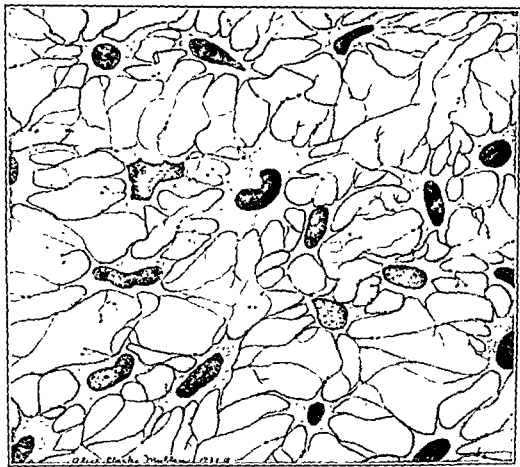

FIG 95.—AREA OF WHOLE MOUNT OF THIN TRANSPARENT PLATE OF BONE (TURBINATE) FROM NOSE OF DOG.

The osteocytes with anastomosing processes are visible. The cells occupy lacunae, the processes lie in the canaliculi; the dots represent cross-cut processes. ×810.

outer circumferential lamellae are firmly bound together by collagenous and elastic fibers which pass from the periosteum into and through the superficial lamellae; these are known as the *perforating fibers of Sharpey.* Similar fibers connect together the concentric and interstitial lamellae. The perforating elastic fibers are frequently surrounded by an envelope of fibrous connective tissue.

Bone Marrow.—Bone marrow consists of a variety of connective tissue, largely reticular, which is rich in fat cells and blood vessels and which also contains osteogenic and hemogenic elements, the marrow cells or myelocytes. According to

Nerve endings have not been demonstrated in compact bone nor in the articular cartilages. In the periosteum terminal nerve fibrils are supplied to the musculature of the blood vessels, and other sensory fibrils end in lamellar corpuscles.

Development.—Bone tissue makes its appearance relatively late in fetal life. The long bones are first mapped out by masses of hyaline cartilage. The entire skeleton, with the exception of the flat bones of the face and those of the vault of the skull, is thus primarily formed by plates of fetal cartilage. The process by which these cartilaginous plates are transformed into bone is known as *intracartilaginous* or *enchondral ossification*. The process is essentially one of replacement of cartilage by bone, not one of change of cartilage into bone. The resulting bones are known as *substitution bones.*

The flat bones of the face and skull (including the interparietals, parietals, frontal, squamosals, tympanics, median pterygoid plate of the sphenoid, nasals, lacrimals, malars, palatines, vomer, maxilla, and a portion of the mandible) are formed directly from the mesenchymal blastema without the intervention of cartilage. This method of bone formation differs somewhat from the above and is known as *intramembranous ossification.*

Intracartilaginous Ossification.—This process begins with the formation of plates of hyaline cartilage whose shape corresponds more or less closely with that of the future bone. This type of *fetal cartilage* differs from the hyaline cartilage of the adult only in the irregular form and distribution and greater abundance of its cartilage cells.

Each plate of fetal cartilage is enveloped by a layer of embryonal fibrous tissue, the fetal perichondrium. The outer portion of the fibrocellular layer is destined to become the *periosteum* of the future bone; its innermost portion contains many small round cells, which from their intimate relation to bone production, are known as *osteoblasts*. The inner portion of the perichondrium forms the *osteogenic layer* of the future periosteum.

CENTERS OF OSSIFICATION.—Ossification of the cartilage begins at one or more points which are called *centers of ossification*. In the long bones, in which the process of bone formation can be most readily traced, there are usually three such centers, one near the middle of the cartilaginous plate, from which the diaphysis is formed, and one epiphysial center at each extremity. The centers for the epiphyses make their appearance much later than that for the shaft of the bone, for the most part not until some months after birth, and from an extension of marrow from the primary center.

ENLARGEMENT OF THE CARTILAGE CELLS.—The first indication of beginning bone formation is evidenced by an *enlargement of the cartilage cells* which promptly arrange themselves in rows or columns that radiate from the center of ossification (calcification). This process is accompanied by absorption of the adjacent cartilage matrix, so that the enlarged cartilage cells are contained within broad spaces or *areolae*. The cartilage cells now appear to undergo a gradual but progressive absorption; their cytoplasm becomes shrunken and granular and finally disappears; even the nucleus at last succumbs to the process

as a whole is of course dependent upon the blood, with all its hemal elements.

Osteoblasts.—These are cells which may assume various shapes depending upon their spatial relationship to the bony substance. When free they are of round or slightly oval shape; lining the marrow cavity or covering the bone as portions of the periosteum or applied to spicules of cancellous bone they may become considerably flattened. The nucleus is generally round or oval, deeply chromatic and granular. As spheroidal cells they have an average diameter of about 8 microns. They are with difficulty distinguished from lymphocytes except when characteristically arranged as a membranous coat upon the surface of bony walls or spicules, They become the bone cells of compact bone. Osteoblasts and lymphocytes are genetically closely related, both being relatively slightly differentiated mesenchymal cells.

Osteoclasts.—These are giant multinuclear cells, often containing as many as ten to twenty or more nuclei. They are the cells by whose agency bone is destroyed during the processes of development and growth. They are similar to, but not identical with, the polykaryocytes of hemogenic foci which are concerned with the processes of erythrocyte and platelet formation. The osteoclasts originate by a process of fusion of reticular cells of the marrow; the hemogenic polykaryocytes originate from lymphocytes (hemoblasts) by repeated amitotic division of the nucleus.

Blood Supply.—Marrow, and especially the red variety, is richly supplied with blood. *The nutrient or medullary artery penetrates obliquely through the nutrient foramen* to the marrow cavity of a long bone where it divides into an ascending and descending branch and supplies an abundance of small arteries to all portions of the medulla. The terminal arteries end in broad capillary vessels whose wide lumen and delicate endothelial walls determine their character as *sinusoids*. It was formerly thought that the endothelial walls of these vessels were here and there deficient, and although certain later investigations discredit the former observations, the all-important fact remains that the endothelial walls are pervious to both red and white blood cells. Certain of the terminal arteries anastomose with those of the cancellous epiphyses, and with the arteries which enter the haversian canals of the compact bone from the periosteum.

Efferent veins return the blood from the sinusoidal capillaries of the marrow. These veins, passing as companion veins to the medullary artery through the nutrient foramen, or independently through separate foramina, as also those of the bony tissue, are not supplied with valves. Outside of the bones, however, these same veins contain abundant valves.

The Lymphatics.—The lymphatics of bone occur in great abundance in the periosteum, and as perivascular spaces penetrate the canals of Havers and Volkmann and thus reach the medullary cavity. The existence of lymphatics within the marrow, other than in the sheaths of the blood vessels, is doubtful.

The Nerves.—The nerves accompany the blood vessels in all portions of the bone and marrow and form a rich perivascular plexus which is distributed to the walls of the vessels; occasional side fibrils are also distributed to the marrow.

PRIMARY BONE.—The *osteoblasts* which thus gain access to the primary marrow cavities, now arrange themselves along the surface of the remnants of calcified cartilage and begin the deposit at their proximal surface of the fibrous tissue and calcareous salts which compose the *primary bone*. The osseous matrix is commonly assumed to be the product of an osteoid transformation of the exoplasm of the osteoblasts. Many of the osteoblasts apparently become entangled in this newly formed tissue and form the *osteocytes*. The fetal cartilage is thus transformed into a spongy mass of primary osseous tissue whose spicules are formed by a core of calcified cartilage upon which are deposited successive layers of bony tissue with their included lacunae and bone cells. In sections stained with hematoxylin and eosin, the central strand of calcified cartilage is colored blue, the primary bone, red.

Axial sections of long bones at this stage of ossification show all the above changes in regular succession from the fetal hyaline cartilage at the extremities to the primary bone with its marrow cavities in the center. The process of ossification steadily progresses toward the ends of the bone, the line of enlarged cartilage cells constantly advancing farther and farther from the original center of ossification.

ABSORPTION OF THE NEWLY FORMED BONE.—It is at this stage, however, that the giant cell *osteoclasts* become most active and the *absorption of the newly formed bone* progresses rapidly. The osteoclasts collect along the surface of the spicules of primary bone in considerable numbers and appear to sink into little recesses which they form within the bony tissue. The little bays which are thus formed in the primary bone are the *lacunae of Howship*. The continued absorption soon breaks down and removes the trabeculae and partitions of spongy bone and thus forms a central *medullary cavity* which is found to be of constantly increasing size.

PERICHONDRIAL OSSIFICATION.—Coincident with these changes within the cartilage the osteogenic tissue which forms the inner layer of the perichondrium produces successive layers of bony tissue upon the surface of the fetal cartilage. This process of *perichondrial (periosteal) ossification* proceeds in a manner similar to that by which bone is formed in membrane which is not closely applied to cartilage.

Perichondrial bone formation is essentially of the intramembranous type. In essence there is no valid distinction between endochondral, perichondrial and membrane bone development, since each involves calcification of a fibrillar matrix by agency of the same cell, the osteoblast. At irregular intervals the osteoclasts collect and the primary perichondrial bone is absorbed. Into these cavities buds of vascular osteogenic tissue push their way to form canals of considerable length. Upon the surface of the canals which are thus hollowed out of the perichondrial bone, the *haversian spaces*, the osteoblasts deposit successive concentric layers of bony tissue and the *haversian systems* make their appearance. Finally, upon the surface of the periosteal bone successive layers of newly formed bony tissue compose the *external circumferential lamellae*, while upon the wall of the medullary

CALCIFIED CARTILAGE.—The absorption of the cartilaginous matrix proceeds more rapidly in those portions which separate the individual cells in the columns than in those other portions which intervene between the adjacent rows of cartilage cells. While the former portions are entirely absorbed, remnants of the latter remain, and in them calcium salts are deposited in an irregular manner. *Calcified cartilage,* the most primitive of the calcareous tissues, is thus formed.

PRIMORDIAL MARROW CAVITIES.—The absorption of the cartilage matrix results in the formation of broad spaces into which osteogenic buds of primitive marrow tissue push their way from the perichondrium. Thus the *primordial marrow cavities* are formed. The fetal marrow which now occupies these cavities is derived from the osteogenic layer of the primitive periosteum. The osteogenous

FIG 99—THE PRIMARY CHANGES IN INTRACARTILAGINOUS BONE FORMATION.

A, metatarsus, *B* and *C,* phalanges of human fetus. In *A,* the earliest enlargement of cartilage cells at the center of ossification is shown *B* and *C* are successively later stage. The bones are cut in longitudinal section. Carmine hematoxylin stain. ×27. (Toldt.)

tissue of this layer, containing osteoblasts, osteoclasts, and developing blood vessels, grows into the cartilage in the form of bud-like cords which are preceded by absorption of the adjacent cartilage matrix. This so-called "eruptive tissue" promptly reaches the center of ossification and burrows its way into the enlarged cartilage lacunae whose cells are now replaced by *primary osteogenic marrow.* The destruction of cartilage is initiated and maintained by agency of the osteogenic tissue, presumably through specific cells, the so-called *chondroclasts,* the morphological marks of identification of which are not yet known. According to some investigators [21] the cartilage cells do not disintegrate but pass into the marrow cavity where they become osteoblasts.

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[21] Retterer, 1900.

cavity a similar endosteal layer of bone-forming cells deposits the *internal circum-ferential lamellae*. The haversian canals are actually continuations of the marrow cavity, and the larger are even lined by endosteum.

With the formation of the perichondrial bone the lateral expansion of the organ by endochondral bone formation necessarily ceases. Henceforth increase
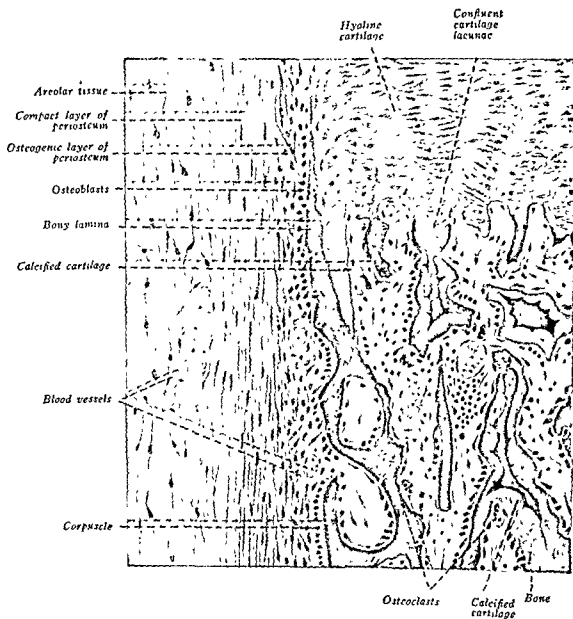
FIG 101 —ENCHONDRAL BONE DEVELOPMENT. (Sobotta.)

in diameter of the bone is only produced by continued absorption internally of the compact bony wall and the formation of new bone beneath the periosteum by frequent repetitions of the processes of periosteal (perichondrial) ossification as already described. The remnants of those haversian and circumferential lamellae which are only partially absorbed in this process form the *interstitial lamellae* of the mature bone. In the long bones and in flat cartilage bones ossifi-

Zone of Enchondral Ossification

Zone of Calcified Cartilage

Cavity Primordium

...al Bone

Primary Marrow

Enchondral Bone

Calcified Cartilage

...! Cartilage
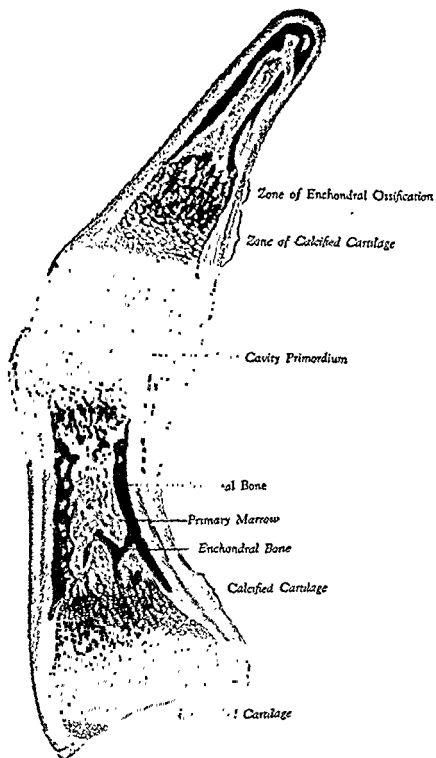
FIG. 100.—A LONGITUDINAL SECTION OF THE TWO DISTAL PHALANGES FROM THE FINGER OF A FIVE-MONTHS' HUMAN FETUS. ×15

(From Sobotta, Histology.)

The following is a *résumé* of the various stages of endochondral ossification:

1. Formation of the fetal hyaline cartilages from precartilage mesenchymal blastema
2. Enlargement of the cartilage cells with a rearrangement into radiating cell rows at the center of ossification
3. Absorption of the cartilage matrix between the cells of the rows and finally also of the cells themselves. Calcification of persistent remnants of cartilage matrix between the rows of cells
4. Eruption of the subperiosteal osteogenic tissue, invasion to center of cartilage plate, and the formation of primary marrow cavities at the center of ossification
5. Gradual extension of the above processes followed by a deposit of primary bone by the osteoblasts upon the calcified cartilage spicules. Coincident osteoblastic deposit of perichondrial bone beneath and within the perichondrium of the cartilage plate
6. Absorption of portions of the primary bone by the osteoclasts to form the large central marrow cavity or medulla. The absorption involves both the endochondral and the perichondrial bone and is accompanied by a further deposit of new bone at the periphery. In the perichondrial bone cylindrical axial channels are formed, in which the deposit of new bone produces the haversian systems of the compact bony tissue

Intramembranous Ossification.—This is the simpler and more direct method of bone formation. In principle it is identical with perichondrial ossification. Endochondral bone development differs from it only in respect of the additional processes involved in the removal and replacement of the hyaline cartilage.

Membrane bones, including the flat bones of the face and the vault of the cranium, arise directly in the mesenchyma. The first indication of ossification is the enlargement and rounding up of a group (or groups) of mesenchymal cells, and their association in the form of an irregular membrane. Among the cells appear bundles of delicate collagenous fibrils, the *osteogenic fibers*, radiating beyond the limits of the cell group. The cells of this initial ossific group begin to function as osteoblasts and deposit osseous matrix among the fiber bundles. This original osseous trabecula marks approximately the center of the future bone. The surrounding loose mesenchyma has meanwhile become increasingly vascular. Vaguely outlining the peripheral limits of the definitive bone appears a relatively thick layer of denser, more cellular mesenchyma, the cells in general maintaining a fusiform shape. This represents the primitive periosteum of the forming bone. The bone takes shape internally by the appearance of numerous trabeculae, which arise in the manner described for the initial spicules and then unite into a bony sponge-like structure inclosing vascular mesenchyma, the primary marrow. The spicules of the *cancellous bone* contain numerous bone cells—the representatives of original osteoblasts which have become enmeshed in their own product of osseous matrix—and are covered with an epithelioid membrane of a single or double layer of osteoblasts, which contribute to the further growth of the bony trabeculae. The marrow includes besides osteoblasts and the specific marrow cells—somewhat less numerous than in the primary marrow of endochondral bone—numerous osteoclasts under whose absorptive agency, assisted by the productive activity of the osteo-blasts, the inner conformation of the growing bone continually alters its details.

cation at first proceeds in the perichondrium, endochondral ossification appearing only later; in the short bones ossification is endochondral until the cartilage is entirely replaced by bone.

EPIPHYSEAL OSSIFICATION.—During the processes of endochondral and peri-chondrial ossification within the shaft of the bone, the epiphyseal cartilages continue to grow. Finally, however, ossification begins in the *epiphysis*, osteogenic tissue having pushed in from the primary center of the diaphysis, and proceeding in the same manner as in the shaft, results in the formation of primary spongy bone, some of which is absorbed and replaced by more compact bony tissue, as occurs in the wall of the diaphysis. In its central portions the tissue retains its
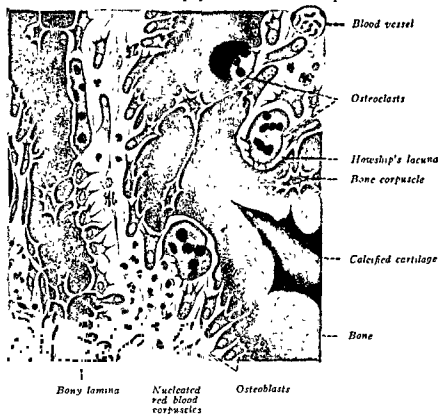
FIG 102.—LATER STAGE IN ENCHONDRAL BONE DEVELOPMENT. (Hardesty.)

spongy arrangement and but few haversian systems are formed. It is thus that the *cancellous bone* of this part, as well as that of the ends of the diaphysis, is formed.

At the point where the expanding centers of ossification of the shaft and epiphysis are about to meet, a line of unossified cartilage, the *epiphyseal line*, persists until growth of the bone is complete. It is by growth of this cartilaginous disk, with continued formation of cartilage mainly on its inner surface, and its concomitant replacement by bone, that the bone increases its length. After ossification of this epiphyseal synchondrosis at about the twenty-first year, growth in length must cease. Meanwhile the perichondrium has become periosteum.

regeneration is said to occur through direct osteoblastic activity, under less favorable conditions a cartilaginous transition stage intervenes. He deduces from his experiments that "diaphyseal bone is reproduced by proliferation of osteoblasts derived from pre-existing osseous tissue, and that its regeneration takes place independently of the periosteum" The periosteum is conceived as being an important factor in determining the conformation and growth limit of bone.

The work of Leriche and Policard [24] confirms the view that the so-called osteogenic layer of the periosteum has no bone-forming function. It is thought to operate simply to arrest and restrict osseous extension. This same work, moreover, presents a new theory of osteogenesis, based upon a large mass of data, histological, experimental and radiographic. The theory supplies a consistent interpretative key for the explanation of various obscure conditions of bone pathology. It resolves the paradox in the current view of osteogenesis which regards the discrete so-called osteoblasts as bone-builders and the multinucleated fusion products of these same cells, in the form of osteoclasts, as bone-destroyers. Osteoblasts are interpreted as osteolytic fibroblasts of more feeble capacity than osteoclasts; their function is said to be to inhibit the spread of osseous tissue. Overwhelmed by the growing bone, they become incorporated as osteocytes. These are generally quite inactive, "useless parasites of osseous tissue," but may be stimulated to function osteolytically under certain pathological conditions. Bone formation is in essence a condition of osseous metaplasia of fibrous connective tissue. The deposition of bone in the fibrous matrix is dependent upon humoral and interstitial, not primarily cellular, factors. Osteogenesis occurs in four stages: (a) edematous infiltration; (b) multiplication of fibrils; (c) conversion of the interstitial fluid into a gelatinous preosseous substance; (d) deposition of calcium phosphates and carbonates in this substance. Bone resorption is said to be the result largely of an osteolysis connected with humoral processes, and only to a small extent the result of an osteoclasia on the part of phagocytic giant cells, the osteoclasts.

Fell [25] reports bone formation in vitro in periosteum from limb bones of six- to ten-day chick embryos. Periosteum from older embryos and young chicks may grow profusely in vitro but it only ossifies in rare cases. Endosteal osteoblasts from haversian spaces of late embryonic and early postembryonic tibial bone readily formed bone in vitro.

Reconciliation of the opposing views regarding the osteogenic capacity of the inner layer of the periosteum is suggested in the publications of Ham.[26] His histologic studies of early phases of bone repair (1930-32) supply fundamental data bearing on the argument about the relative value of periosteum and bone in the process of regeneration "The answer to this problem is that bone tissue is lined on the side of all its haversian canals and its interior by osteogenic cells which are identical with those found in the deep layers of the periosteum. Thus, it is evident that bone tissue, stripped of its periosteum, could reproduce more bone tissue by virtue of its osteogenic cells, which line not only the marrow cavity but also the haversian canals." According to Ham the differentiation of osteogenic cells into bone is dependent upon two factors: the presence of a local deposit of calcium salt and a good blood supply.

JOINTS

Joints are divisible into two main types, the movable and the immovable, or *diarthroses* and *synarthroses*. These and their several modifications call for histologic description. Synarthroses include (a) *syndesmoses*, or joints in which the connecting substance is a dense fibro-elastic tissue joining the bones immovably as in the articulation of the

[24] Leriche and Policard, 1927
[25] Fell, 1932
[26] Ham, 1930-1932

Peripheral osteoblasts, arising from the inner layer of the periosteum, produce the more compact external plates of the bone. In the flat bones of the skull, the central cancellous bone is designated *diploe*, the peripheral compact bone, *tables*. Membrane bones may contain typical haversian systems.[22]
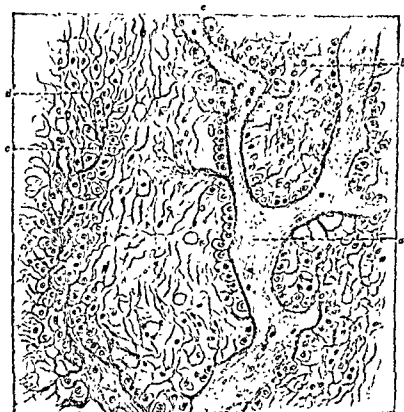

FIG. 103—INTRAMEMBRANOUS BONE FORMATION IN THE LOWER JAW OF A SHEEP FETUS.

a, bone; *b*, primary marrow cavity; *c*, osteoblasts; *d*, growing point of the primitive bone, beyond which primary marrow is developing in the connective tissue ×300. (Bohm and von Davidoff.)

The conditions which determine that certain bones may arise directly in mesenchyma while others must pass through a cartilaginous stage are obscure In general it would seem that those bones which are represented in the skeleton of cartilaginous fishes pass in the higher vertebrates through a cartilaginous stage. The additional bones made necessary by the greater development and larger size of the brain in higher vertebrates, that is, certain bones of the skull and the face, develop as membrane bones

It is commonly believed that periosteum is essential for bone regeneration, and its preservation is aimed at where new growth is desired after osteotomy. But according to W. Macewen,[23] who has made a comprehensive experimental study of osteogenesis in regenerating bone in dogs, the periosteum functions simply as a confining, nutritive, and protective membrane, but has no osteogenic significance His observations lead him to conclude also that in the long bones the osteoblasts are derived from proliferating cartilage nuclei freed from the disappearing matrix. Under more favorable conditions

[22] Arey, 1919.
[23] Macewen, 1912.

CHAPTER IV

MUSCULAR TISSUE

Muscular tissue consists essentially of protoplasm in which the general vital property of contractility has become predominant. However, the path of contraction is practically limited to one direction, the long axis of the cell. This phenomenon of contractility results from the differentiation of specially contractile fibrils, the *myofibrils*, from the protoplasm of embryonic muscle elements, the *myoblasts*. The protoplasm of the muscular tissue is called *sarcoplasm*. Adult muscular tissue may be divided into three classes: smooth, cardiac and striated. All three types arise from mesoderm, with the exception of the dilator and sphincter muscles of the iris of the eye, and the muscle of the secretory portion of the sweat gland—both of the smooth variety—which are generally believed to be of ectodermal origin. In invertebrates muscle tissue may be largely derived from the ectoderm and even from the entoderm.

The smooth muscle is in general limited to the viscera; it is not under the control of the will, hence also called involuntary (nonvoluntary) muscle. The cardiac type is limited to the heart, and to the middle layer of the roots of the aorta, pulmonary artery, and pulmonary veins. It is striated, but like smooth muscle, controlled by the sympathetic nervous system; therefore independent of the will, hence also of involuntary type. Striped, striated or skeletal muscle is practically limited to the skeleton, and subserves the function of skeletal movement. This group includes also the muscles of the eyeball, the ear, the upper third of the esophagus, the diaphragm, and tongue. It is under the control of the will, hence designated voluntary. The striped muscle of the diaphragm and the esophagus is apparently only partially voluntary.

It is obvious from the above that there is demanded a more specific terminology: involuntary smooth (unstriped), involuntary striped (cardiac), and voluntary striped (skeletal). The three types pass through very similar, perhaps identical, earlier stages of histogenesis. The essential difference seems to be one of degree of differentiation. In general, skeletal muscle is most highly differentiated, cardiac muscle being intermediate between smooth and the voluntary striped type.

For a proper understanding of the structure of these three types it is necessary that we now consider the process of muscle histogenesis. The student should gather the several criteria by which he may distinguish between smooth, cardiac and skeletal muscle, both in transverse and longitudinal sections.

skull (*sutura*), or where it consists of ligamentous tissue permitting slight movement as between the lower ends of the tibia and fibula; and (*b*) *synchondroses*, in which the connection is effected by cartilage, either hyaline (*e.g.*, between the epiphysis and diaphysis of young bones) or fibrous (*e.g.*, the intervertebral disks of the vertebral column).

In relation with diarthroses are in several instances (mandibular, lower radioulnar, costosternal, sternoclavicular, acromioclavicular) intra-articular *menisci* of fibrocartilage; here the articular cartilages of the bones concerned are also of the fibrous variety. The semilunar cartilages of the knee and the glenoid cartilage of the shoulder joint are also of the fibrous type. These cartilages serve to deepen the sockets in which the respective ends of femur and humerus move and are known as adaptation cartilages or *labra glenoidalia*.

The joint cavity of a diarthrosis is enveloped in a capsule consisting of two layers, an outer fibro-elastic continuous with the periosteum and an inner cellular layer, the *synovial membrane*, consisting of epithelioid cells forming a mesenchymal epithelium. The function of the synovial membrane is to secrete a lubricating fluid, the synovia, consisting of about 94 per cent water with small amounts of mucoid substances and oil. In the large joints the synovial (serous) membrane is thrown into villus-like folds (Fig. 245). The covering cellular membrane is occasionally imperfect; the cells vary from the flattened, typical mesothelial cells, to the cubic variety, and rest directly upon a vascular, frequently fatty, fibrous stroma. Normal human synovial fluid is a dialysate from blood plasma and contains proteins, globulins and mucin. (Ropes, M. W., Rossmeisl, E. C. and Bauer, W., 1940, *J. Clinical Investigation*, 19:795).

the central fibrils, others claiming that they have a contractile rôle similar to the central myofibrils. Whatever their complete function may be, they certainly seem to bind, together with the connective tissue, the individual cells into a compact tissue in which coördinated movement, as in peristalsis of the intestine, becomes possible—an obviously important condition.

The oval or rod-shaped nucleus retains its central location, and is surrounded by a mass of granular, relatively undifferentiated sarcoplasm, containing mito-

FIG. 105—SMOOTH MUSCLE CELLS FROM THE WALL OF THE HUMAN INTESTINE.
Longitudinal section. Hematein and eosin. ×665.

chondria, lipoid, and glycogen granules. It changes its shape with the phase and degree of contraction, occasionally even assuming a short, spiral form. It has been shown that during contraction the nucleus decreases markedly in length and increases in thickness; and that the uniformly distributed chromatin granules stream toward the poles, where they collect in coarse strands.[2] This structural intranuclear change is apparently unaccompanied by any change in volume.

Smooth muscle cells vary greatly in size—from the shortest of about 50 microns, to some of 500 microns in length in the pregnant uterus. Because of their slender girth and relatively great length these cells are commonly designated *fibers*. When in the contracted condition, they show a number of broad, more deeply staining *contraction nodes* (Fig. 136, *a*), very conspicuous in the smooth muscle of the lower portion of the esophagus. As seen in transverse section these fibers vary in size from a mere point up to their maximum diameter, according as the section happens to pass through the end or through the middle of a fiber. Because of its central location, the nucleus is only found in the larger transections.

FIG 106. — SMOOTH MUSCLE CELLS FROM THE WALL OF THE HUMAN INTESTINE.
Transection. Hematein and eosin. ×750.

Smooth muscle cells may be joined together in interlacing groups as in the wall of the uterus or bladder; or they may form broad membraneous layers as in the wall of the alimentary tract; or again, they may form small isolated bundles, as in the skin. In any case, the muscle bundles are united by a delicate network of connective tissue.

Smooth muscular tissue occurs chiefly in the walls of the hollow or tubular viscera. Its distribution may be classified as follows:

[2] McGill, 1909

HISTOGENESIS AND STRUCTURE

Smooth Muscle.—As stated above, the germ layer involved in muscle histogenesis is the mesoderm. Smooth muscle is derived chiefly (exception: musculi arrectores pilorum) from the visceral or splanchnic layer. This is at first an epithelial structure of a single layer of cells, the primitive mesothelium. The cells subsequently proliferate and change their shape in general to a fusiform type.

Intercellular connections (cytodesmata) are either maintained or established and the tissue is permanently more or less in a syncytial condition. These so-called *intercellular bridges* are particularly pronounced and can be readily demonstrated in the tunica media of the blood vessels of the umbilical cord. It must be emphasized, however, that the outlines of the genetic units in smooth muscle are always distinct, whereas in striped, including the cardiac type, the outlines of the original myoblasts are lost.

The early myoblast, of short spindle shape with central oval nucleus, contains a granular cytoplasm, limited by a delicate membrane, the *sarcolemma*. The granules may be called *myochondria;* whether identical with cytomicrosomes or with mitochondria, whether of cytoplasmic or of nuclear origin, are disputed points. No evidence of a distinct spongioplasm is discernible. This observation tends to invalidate the teaching of certain histologists, that the contractile fibrils (myofibrils) represent modified spongioplasmic threads arranged in rectilinear meshes. Moreover, it has been established by direct observation that the myofibrils arise through process of alignment and subsequent fusion of the myochondria. McGill [1] recognized two types of myofibrils, namely, stouter peripheral *border fibrils* (myoglia) which may pass beyond the limits of a cell and form intercellular bridges; and the more central, or *myofibrils* proper, which are limited to the cells proper and are considerably more delicate. She believed that border fibrils may subsequently arise by fusion of the more delicate fibrils. Coarser fibrils may produce finer fibrils by a process of longitudinal fission.

The function of the border fibrils is disputed, some claiming that they serve to straighten the cell following contraction produced by
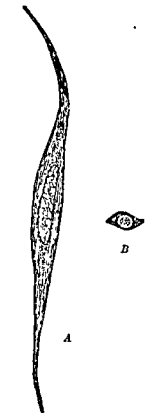
FIG 104—SMOOTH MUSCLE CELLS

A, an isolated cell from the cat's intestine. The nucleus is surrounded by coarsely granular sarcoplasm, continuous peripherally with the finely granular interfibrillar sarcoplasm The innermost myofibrils may erroneously suggest a cell membrane. The fusiform element is invested by a true cell membrane, or sarcolemma. ×750 *B,* oblique transverse section of a cell from the lamina muscularis mucosae of the cat's esophagus. The perinuclear sarcoplasm has contracted away from the nucleus leaving a clear space limited by a sharp line, external to which lies the perinuclear granular sarcoplasm. ×750.

Small numbers of branching cells have been described in the walls of the urinary bladder and the large arteries.

Cardiac Muscle.—Heart muscle takes origin from splanchnic mesenchyma which becomes modified into a loose-meshed syncytium, in which all trace of the original cellular element is lost. The myoblast areas of stellate and irregular form contain a central oval nucleus and a finely granular cytoplasm. In a manner similar to that described for smooth muscle histogenesis, the myochondria form myofibrils which extend for great lengths throughout the sarcoplasmic meshwork. In cardiac muscle the myofibrillae subsequently acquire a cross striation. Adult muscle consists of stouter muscle fibers or trabeculae joined into an intricate close meshwork, by means of less robust branches. The nuclei retain their axial position in the fibers and are surrounded by an oval area of undifferentiated
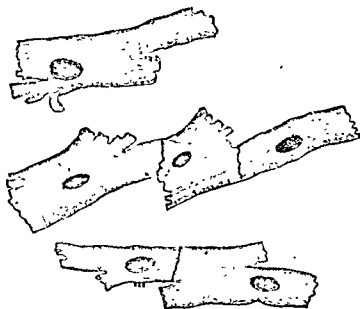

FIG 109—CARDIAC MUSCLE "CELLS" FROM THE PIG'S HEART, ISOLATED IN EQUAL PARTS OF ALCOHOL, GLYCERIN AND WATER.

Unstained. (The nuclei are somewhat darker than they actually appear.) ×410.

granular sarcoplasm. The cardiac fibers and their branches contain peripheral myofibrils, which during growth of the muscle arise by longitudinal splitting of the original fibrils and take position progressively toward the center. Cardiac muscle thus consists of a slender axial core of undifferentiated sarcoplasm swelling to an oval, more expansive mass where the nuclei are located; this core is surrounded by successive rows of myofibrils arranged in radial groups as seen in transverse section; and the whole is invested by a delicate sarcolemma. The striations of the fiber result from the fact of a transverse alignment of identical areas in adjacent fibrillae. The sarcoplasm contains mitochondria (Fig. 108), lipoid, albuminoid (interstitial granules of Kolliker), and glycogen granules. Fat granules ("liposomes"), of probably nutritive significance, and varying greatly in amount according to the functional condition of the individual, are normally pres-

1. In the *alimentary tract:* lower portion of the esophagus, stomach, small and large intestines.

2. In the *respiratory system:* trachea and bronchial tubes.

3. In the *genito-urinary system:* ureter, bladder, urethra, penis, prostate, vagina, uterus, oviduct and ovary.
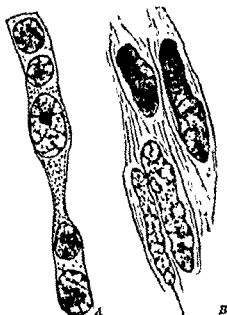
FIG 107—TWO STAGES IN THE HISTOGENESIS OF SMOOTH MUSCLE, FROM THE WALL OF THE ESOPHAGUS OF A PIG EMBRYO.

A, 10 millimeter stage of development The central nucleus of the mesenchymal syncytium has become enlarged and is enveloped by a greater mass of cytoplasm. It represents a myoblast: the peripheral myochondria have become aligned preparatory to fusion to form a muscle fibril. *B,* 21 millimeter stage of development Four adjacent myoblasts, with peripheral stouter myoglia fibrils and central more delicate myofibrils. ×1500.
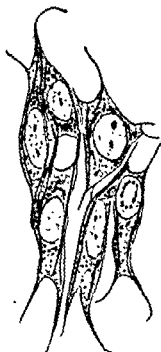
FIG. 108.—A GROUP OF MYOBLASTS FROM THE HEART MUSCLE SYNCYTIUM OF A FORTY-EIGHT-HOUR CHICK EMBRYO.

Showing myofibrils, myochondria and mitochondria. The latter are the deeper staining granules. Meves' technic. ×2000.

4. In the *vascular system:* arteries, veins, and the larger lymphatic vessels.

5. In the *ducts of all secreting glands:* bile ducts and gallbladder, and the ducts of the pancreas, salivary glands, testicle, etc.

6. It is also found in the capsules of the spleen and lymph nodes, in the skin, and in the *intrinsic muscles of the eye.*

Small numbers of branching cells have been described in the walls of the urinary bladder and the large arteries.

Cardiac Muscle.—Heart muscle takes origin from splanchnic mesenchyma which becomes modified into a loose-meshed syncytium, in which all trace of the original cellular element is lost. The myoblast areas of stellate and irregular form contain a central oval nucleus and a finely granular cytoplasm. In a manner similar to that described for smooth muscle histogenesis, the myochondria form myofibrils which extend for great lengths throughout the sarcoplasmic meshwork. In cardiac muscle the myofibrillae subsequently acquire a cross striation. Adult muscle consists of stouter muscle fibers or trabeculae joined into an intricate close meshwork, by means of less robust branches. The nuclei retain their axial position in the fibers and are surrounded by an oval area of undifferentiated

Fig 109—Cardiac Muscle "Cells" from the Pig's Heart, Isolated in Equal Parts of Alcohol, Glycerin and Water.

Unstained (The nuclei are somewhat darker than they actually appear.) ×410

granular sarcoplasm. The cardiac fibers and their branches contain peripheral myofibrils, which during growth of the muscle arise by longitudinal splitting of the original fibrils and take position progressively toward the center. Cardiac muscle thus consists of a slender axial core of undifferentiated sarcoplasm swelling to an oval, more expansive mass where the nuclei are located; this core is surrounded by successive rows of myofibrils arranged in radial groups as seen in transverse section; and the whole is invested by a delicate sarcolemma. The striations of the fiber result from the fact that a transverse alignment of identical areas in adjacent fibrillae. The sarcoplasm contains mitochondria (Fig. 108), lipoid, albuminoid (interstitial granules of Kolliker), and glycogen granules. Fat granules ("liposomes"), of probably nutritive significance, and varying greatly in amount according to the functional condition of the individual, are normally pres-

Fig. 110—Longitudinal Section ... ... Muscle.

GS, intercalated disks; A, branching fibers; K, nuclei; S, cent... sarcoplasm; Z, connective
tissue cell ×380 (Schaffer)

ent in cardiac muscle.[3,4] This fatty content can be demonstrated by the several
microchemical techniques for lipoids. According to Meves, Duesberg, and others,
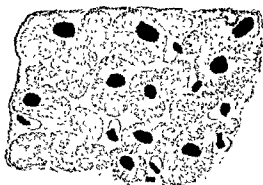
Fig 111—Transection of a Group of
Cardiac Muscle Fibers from a
Papillary Muscle of the Human
Heart.

Hematein and eosin ×550.

the myofibrils of striped muscle differentiate
from the mitochondria of the myoblasts;
but since mitochondria can be demonstrated
in highly developed fibers (Fig. 118) it
seems improbable that mitochondria have
anything directly to do with the develop-
ment of muscle fibrils.

It has been claimed that heart muscle
and striped muscle generally can be in-
terpreted in terms of muscle cells, and
intercellular myofibrillae, in analogy with
connective tissue. But the presence of a
continuous axial core of undifferentiated
sarcoplasm in heart muscle, lack of a defi-
nite cell membrane separating this sarco-
plasm from the outlying myofibrillae,
inability to separate such cells by dissociation methods, and the extension of the
telophragma to the nuclear wall, seem to render this view untenable.

3 Bell, 1911.
4 Bullard, 1912.

The myofibrils must be considered further. No distinction between border fibrils and central fibrils, as in smooth muscle, is possible in cardiac muscle. But the myofibrils undergo greater differentiation. This expresses itself in an alternation of light and dark disks (bands, segments, stripes), said to consist of isotropic and anisotropic substances respectively. While the disks are conspicuous both in fresh and stained tissue, the demonstration of their physical properties under the polariscope is a matter of difficulty. Under crossed Nicol prisms the entire fiber appears lighter than the field, showing the presence of anisotropic materials (granules) scattered throughout the fiber, but a definite banding corresponding to the light and dark disks of fresh muscle is not apparent in all striped muscle under certain conditions. It seems more probable that, though anisotropic substances are more abundant in the dark disk, they are not absent in the lighter disk; moreover, they are more or less definitely aggregated in the dark disk according to the phase of contraction. Furthermore, it is now generally believed that anisotropy only signifies a special *condition* of the sarcoplasm rather than the presence in sarcoplasm of a specific *substance*. According to this interpretation the anisotropy of the dim disk is the result of the arrangement of the ultramicroscopic constituent particles or molecules of the Q substance with their long axes all in the same direction, parallel with the line of tension.

Fig. 112.—CARDIAC MUSCLE FIBERS.

A, portion of a fiber from a macerated preparation of a cat's heart, drawn according to its appearance in the optical longitudinal plane. Two nuclei are shown, connected by a continuous axial strand of coarsely granular sarcoplasm. The sarcolemma appears festooned between successive ground membranes. There is no evidence of a cell membrane separating the central granular from the peripheral non- or finely-granular sarcoplasm ×1000. *B*, median longitudinal section of a fiber from the ventricle of an adult white mouse. Note the continuity of the axial sarcoplasm. These fibers are in contracted condition. ×1000.

The lighter (clear) disk, or intermediate disk of Krause, is commonly designated by the letter J (Isotrope streife); the dark (dim) disk, or transverse disk of Brucke, by the letter Q (Querscheibe). On closer inspection the J disk is seen to be bisected by a dark disk or membrane, the ground membrane of Krause, designated by the letter Z (Zwischenscheibe).

The term *telophragma* was employed by Heidenhain in 1911 for this membrane. The myofibrils are intimately connected with it. Similarly, the Q disk is bisected by a narrow light disk, the median disk of Hensen (H), which in turn is said to be bisected by the intermediate membrane of Heidenhain, or *mesophragma* (M, Mittelscheibe). Both telo- and mesophragmata (inophragmata) are supposed to unite with the sarcolemma peripherally, and to be structurally similar. The telophragma is in intimate connection both with the sarcolemma and the nuclear membrane. But the

mesophragma, at least in cardiac muscle, is not a true membrane to which the fibrils are attached in the manner of the telophragma. Indeed it remains an open question whether heart muscle actually possesses a mesophragma.

The portions of a fibril, or *sarcostyle*, included between successive telophragmata, constitute structural units, the *sarcomeres*, or *inokommata* (Heidenhain, Fig. 113). These same terms are used also to designate the portions of the fiber as a whole between successive telophragmata. In macerating fluids fractures occur
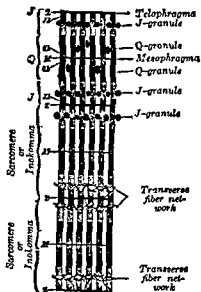
FIG. 113—DIAGRAM OF A STRIPED MUSCLE FIBER, ACCORDING TO HEIDENHAIN.

The transverse fiber network may be a trophospongium.
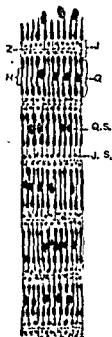
FIG. 114—LONGITUDINAL SECTION OF PORTION OF WING MUSCLE FIBER OF MANTIS, AT MIDPHASE OF CONTRACTION.

Z, telophragma; *H*, Hensen's disk; *J*, isotropic disk; *Q*, anisotropic disk; *Q. S.*, q-sarcosome; *J. S.*, j-sarcosome. ×1600.

at the Z lines. These membranes extend completely across the fiber, through the axial strand of sarcoplasm—a significant fact controverting the cellular idea of cardiac muscle originally advanced by Apathy. The interstitial granules of Kolliker (sarcosomes of Retzius) scattered throughout the Q and J disks in striped muscle, both cardiac and skeletal, are designated the Q and J granules respectively (Holmgren).

Intercalated Disks.—A unique characteristic of cardiac muscle pertains to the presence of the *intercalated disks* (junctional lines) or bands of Eberth. These are barely visible in ordinary histologic preparations, but can be rendered conspicuous by the special technics of Heidenhain and of Zimmermann. In gross appearance they are of several sorts: straight bands, step-like forms, and serrated forms.

The bands (disks) may extend completely across a fiber, or only the width of a single fibril (granule type); the step form may consist of one or more groups of steps and risers, the risers being the height of one or, occasionally, several inokommata; the saw-tooth type also may be of small or greater extent, and of the height of one or several inokommata. All three types may be arranged in rings or even longer or shorter spirals. The intercalated disks are peripheral in position, extending for varying depths, but never completely through a fiber, and never central to the axial sarcoplasm. They are occasionally on the same level with the nucleus. They have been found in the heart of representatives of all the animal groups to, and including, teleost fishes.[5] They are present sparsely and in simple form also in the heart of Limulus. They are probably a morphologic incident of the rhythmic contraction of cardiac muscle. They appear only late in fetal life, toward the end of the last week of gestation in the guinea-pig.

The earliest disks are of the coarsely granular band type. Subsequently they increase in number and complexity, the older stages being characterized by occasional saw-tooth forms. Once formed, they are evidently for the most part permanent structures, undergoing modification largely through mechanical factors. On closer inspection, under the higher powers of the microscope, they are seen to consist of units corresponding to portions of a single fibril These units may be granular or compact. The units are bisected or bounded on one side by the Z membrane. Association of the units in transverse lines gives rise to the band forms; they may be drawn into spirals by longitudinal traction of the fibers involved; unequal transverse and oblique tractions probably produce the step forms, the saw-tooth form arises by process of longitudinal splitting of fibrils, enlargement of fibers, and the various tensions characteristic of hypertrophying fibers. The exclusive type of hypertrophied heart muscle is the more or less complex saw-tooth type. The practically exclusive type of atrophied heart muscle is the comb type, a type produced from a band type by a modification involving longitudinal tension (Fig. 116). In brief, the unit of structure is a modified locus on a myofibril, in essence involving an accumulation of granules about the Z membrane. Such foci associated in various ways produce the various types of bands and steps, the latter in part due also to external mechanical factors, the extreme condition of such effect being saw-tooth forms.

FIG 115.—LONGI-
TUDINAL SEC-
TION OF POR-
TION OF ATRIO-
VENTRICULAR
BUNDLE OF
HEART OF BEEF.

A significant point concerns the similarity between the phylogenetic and ontogenetic development of intercalated disks: that is, below birds, as in all fetal hearts, only simple bands appear; in birds, as in young hearts, step forms are present, only in mammals and in old hearts do the more complex types appear. What then is the meaning of these disks? Any interpretation must be more or less tentative at present. It is easier to say what they probably are not, than what they probably are. They were originally interpreted as cell boundaries, or intercellular cement lines (Schweigger-Seidel); this interpretation has recently been again supported by Zimmermann. This interpretation would mean that from a syncytium a cellular tissue has secondarily arisen by the appearance of cement lines, secondary cells having been formed in a syncytium, irrespective of the original genetic units. A number of facts render this inter-

Many of the cells are binucleated. ×160.

[5] Jordan and Steele, 1912

pretation inadmissible, chief among which are their occasional supernuclear position, and their peripheral location. A more recent interpretation conceives of them as places where the muscle fiber grows, that is, as sarcomeres in the making (Heidenhain). Among the countervailing facts to such interpretation are chiefly the absence of transition stages, their relative scarcity at the period of greatest growth of the heart, and their continued abundance in full-grown, even aged, hearts. The suggestion has been made that they are related to a phase of contraction. This seems more likely. Since, once formed, disks are largely permanent, and undergo subsequent modification, they must represent an *irreversible* condition of the contraction phase. The interpretation of the disks, as *irreversible contraction bands*, rests upon the similarity of the simplest types and the contraction bands of Rollet, both characterized by accumulation of dark staining granules about the Z membrane. In the older hearts, where they are mechanically modified, and in diseased hearts, as in hypertrophies, where probably a chemical modification is superposed, they represent lines of weakness. These are the locations of fracture in fragmented and segmented pathological hearts.

Heart muscle is syncytial in structure, and the myofibrillae pass uninterruptedly through the intercalated disks. These facts are of special importance because of
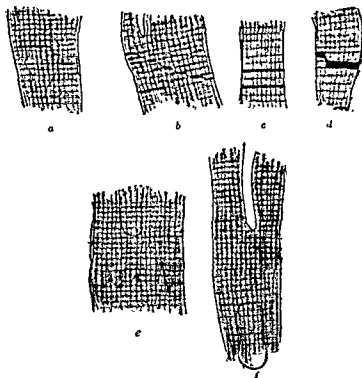
FIG 116—VARIOUS TYPES OF INTERCALATED DISKS.

a, from guinea-pig's heart; *b*, from chipmunk's heart; *c*, from monkey's heart; *d*, from monkey's heart; *e*, from guinea-pig's heart; *f*, from chipmunk's heart ×1200.

their bearing on the opposed theories of the origin and conduction of the stimulus to the heart beat, the *myogenic* and the *neurogenic*. A complete cellular structure with actual cement lines, combined with the fact that the atria are apparently com-

pletely separated from the ventricles by intervening connective tissue, was once urged as a strong argument against the validity of the myogenic theory of heart beat —the theory which proclaimed the adequacy of heart muscle to initiate and conduct the stimulus to contraction without the intervention of nerve elements, that is, to beat automatically and independently of the nervous system. The neurogenic theory, which holds that the nerve elements are essential for the conduction of stimuli for contraction, on the other hand, seemed contradicted by the observation that in the chick the heart beat rhythmically before the appearance of nerve fibers. However, there remained the possibility that nerve fibers were present but undemonstrable by the method employed; also that while nerves might be unnecessary for maintaining rhythmic contraction during embryonic life, they nevertheless became necessary in fetal and adult life

The discovery of the *atrioventricular bundle of His* (1893) at first added apparently the strongest evidence to the support of the application of the myogenic theory of heart beat in the mammalian forms This is a muscular bundle which effects an intimate connection between the atria and the ventricles. See Figure 227.

An important matter is the observation that the final ramifications of the bundle of His are identical with the so-called *Purkinje fibers*. These have long been known, especially in the sheep's heart, where they are unusually large and abundant. They are limited to a region directly under the ventricular endocardium. They are coarser, less branched, with fewer intercalated disks, almost exclusively of the band type, than are the fibers of the myocardium proper. They would seem to represent a younger or less highly differentiated stage of muscle fiber. In cross-section they are of greater diameter, with fewer peripheral myofibrils and a far greater amount of central undifferentiated sarcoplasm, rich in glycogen. According to Lange,[6] the Purkinje fibers cannot, however, be regarded as remains of embryonic muscle cells, since they are clearly distinguishable already in very young mammalian embryos; they constitute the non-nervous apparatus for conducting stimuli to heart beat.
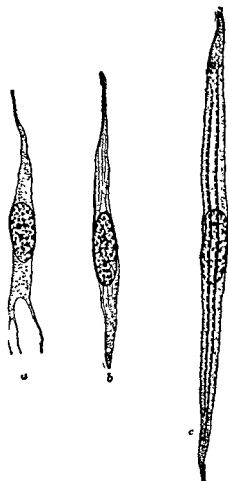
FIG. 117.—SUCCESSIVE STAGES OF SKELETAL MUSCLE HISTOGENESIS IN MAMMALS.

a, myoblast with fine cytoplasmic granules (myochondria), from a 13 millimeter sheep embryo; *b*, myoblast with homogeneous myofibrils, from a 10 millimeter guineapig embryo; *c*, myoblast with cross-striped fibrils, from a 8.5 millimeter rabbit embryo (From Heidenhain, after Godlewski.)

[6] Lange, 1914.

The myogenic theory accordingly seemed well established. It was apparently strongly supported by the experiments of Erlanger,[7] who clamped the bundle in the dog's heart and produced a condition of heart block—a disturbance of the coördinated rhythmicity of the atria and ventricles—*without, however, interfering with the conduction of impulse*, since there resulted no stoppage of contraction in the ventricles. But the subsequent discovery of abundant nerve fibers and ganglion cells (Tawara, Wilson, McGill) in the bundle, intimately related to the cardiac fibers, robbed this experiment of its specific applicability and seemed for a time to force an interpretation favoring the neurogenic theory. Carlson,[8] moreover, demonstrated its validity for the Limulus heart, which, after the removal of its ganglion, could not be made to beat. But Burrows[9] has shown that single cells of a fourteen- to eighteen-day embryo chick heart, grown in artificial culture media, may begin to beat automatically and rhythmically—an observation which would seem to settle the point that heart muscle may beat rhythmically in the absence of nerve supply or even nerve stimulus.

Furthermore, Hooker[10] showed that *in the frog larvae in which the nervous system was entirely removed, the cardiac muscle will differentiate and function normally, independently of nervous control* The myogenic theory is further supported by the fact that it has been possible to revive the excised heart of man to rhythmic activity twenty hours after death,[11] whereas the longest time that a nerve cell is known to survive (in the intestine) is three and one-half hours.[12] In the superior cervical ganglia, nerve cells may survive one hour, while in the brain the maximum time of survival is said to be fifteen minutes.

Fig. 118.—Transverse Section of a Striped Muscle Fiber of a Newly Hatched Rainbow Trout, Showing the Process of Myofibril Increase by Radial Longitudinal Splitting.

Mitochondria are seen in the peripheral sarcoplasm and around the nucleus at the right Meves' technic. ×2000

Any interpretation of the intercalated disks as actual intercellular structures (cement substance) is inconsistent with the myogenic theory of the heart beat, which now seems largely to prevail. The present status of the matter seems to be that the origin of stimulus to heart beat in vertebrates is myogenic, in invertebrates probably neurogenic. The difference may inhere in the absence in the hearts of invertebrates of a muscular coordinating structure analogous to the atrioventricular bundle of vertebrate hearts.

Voluntary Striped or Skeletal Muscle.—The unit of structure of skeletal muscle is essentially the same as that described for cardiac muscle, namely, a myofibril or *sarcostyle*. Huber[13] has shown that the myofibrils of one fiber may pass to an adjacent fiber. Thus voluntary striped muscle also is syncytial, in a manner similar to smooth and cardiac muscle. The fiber and the constituent fibrils are likewise divisible into successive sarcomeres or inokommata. A difference in detail inheres in a greater definiteness of striation, and a greater complexity, due to the presence generally of an additional disk in the J stripe. This stripe or *accessory disk* of Engelmann (N line; Nebenscheibe) bisects the portion of the J disk between the Z line and the succeeding Q disk. It is interpreted more or less

[7] Erlanger, 1906
[8] Carlson, 1904.
[9] Burrows, 1911.
[10] Hooker, 1911.
[11] Flack, 1909
[12] Cannon and Burkett, 1913.
[13] Huber, 1916.

tentatively by Heidenhain as due to a linear arrangement of J granules. However, apart from the possible presence of interfibrillar J granules the fibrils themselves may be locally modified, such modification constituting the true N disk.[14] This disk may represent a lagging portion of the Q substance during or following contraction.

The median segment of the J disk, that is, the portion between the N line and the Z line, is called the *terminal disk* by Merkel (E disk; endscheibe). This complex condition of striping is conspicuous only in the leg muscle of certain insects. Complexity of striation appears to be correlated with an ability to contract only slowly but with great force. Rapidity of contraction, and the ability to sustain rapid function for long periods of time, as in the wing muscles of certain insects and the analogous pectoral muscles of birds and bats, is correlated with a relatively very coarse sarcostyle and a relatively simple condition of striations. The wing muscles of certain insects may perform as many as 300 complete contractions in a second. In routine laboratory preparations only the Z, Q and J disks are readily discernible. The occurrence of an N disk
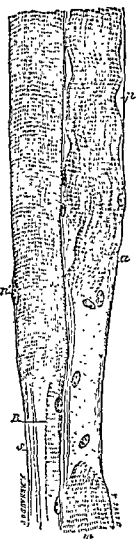
FIG. 119
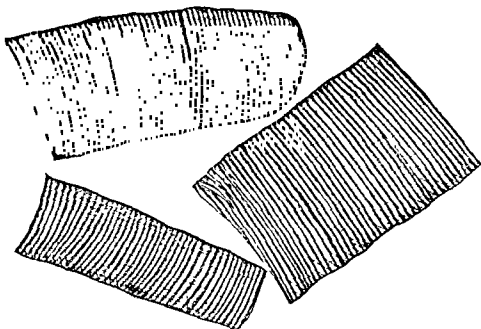
FIG. 120

FIG 119—STRIATED MUSCLE FIBERS RUPTURED BY TEASING, SHOWING THE SARCOLEMMA.

a, ruptured end of the muscle fiber; *b*, a bundle of fibrils projecting from the torn end; *m*, a muscle fiber; *n'*, a nucleus of the muscle cell; at *p*, the muscle substance has shrunken away from the sarcolemma; *s*, sarcolemma. Moderately magnified. (Ranvier.)

FIG 120—ISOLATED FRAGMENTS OF STRIATED MUSCLE FIBERS, UNSTAINED.

The one above is from the end of a fiber; that on the right shows at one end a tendency to cleavage into transverse disks. ×360.

[14] Speidel, 1939

may possibly be associated with a stage in the formation of the contraction band in muscle which contracts only slowly but very forcibly.

In skeletal muscle the myofibrils are more or less sharply aggregated into small groups, known as Kölliker's columns. In transverse sections of the fibers these columns appear as irregular granular areas, the so-called areas of Cohnheim. Each group or column represents the final division products of an earlier coarser fibril (Fig. 119). In view of the increasing confusion regarding the identity of
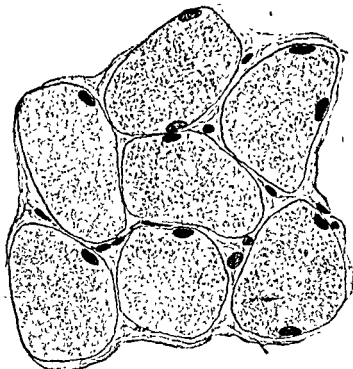
FIG. 121.—STRIATED MUSCLE FIBERS OF THE DOG, SEEN IN TRANSECTION.
The areas of Cohnheim are indistinctly outlined. Hematein and eosin. ×490

"Cohnheim's areas" it seems preferable to use the term "Kölliker's areas" to designate the transverse sections of Kölliker's columns. These are equally conspicuous whether the section passes at the level of adjacent Q disks or J disks. In this, the usually accepted sense "Cohnheim's areas" do not represent transverse sections of groups of myofibrils at Q levels alternating with groups cut at J levels, as recently proposed by Carey and Zeit.[15] The "areas" are transverse sections of groups of fibrils (Kölliker's columns); their borders are regions of fibril-free sarcoplasm.

Another difference between skeletal and cardiac muscle pertains to the diameter of the fiber and the position of the nucleus. In skeletal muscle the fiber has a greater diameter, is more nearly circular in cross-section, the myofibrils are scattered throughout its diameter, and the nuclei are peripheral, lying just beneath the sarcolemma. The nuclei are enveloped in a small amount of granular sarcoplasm.

[15] Carey and Zeit, 1936

The sarcolemma is a homogeneous, plastic, non-nucleated membrane, the representative and product of the cell membrane of the original myoblasts.

The perinuclear sarcoplasm contains filar and granular mitochondria. Both the

FIG. 122.—LONGITUDINAL SECTION OF SKELETAL MUSCLE OF CAT.

The cross-striations (disks) include the dark Q stripes, the alternating light J stripes and the dark ground (Z) membranes bisecting the J stripes. ×875. This muscle is in relaxed condition.

perinuclear and interfibrillar sarcoplasm contains also fat granules and globules (liposomes), interstitial granules of Kölliker and glycogen.

Heidenhain [10] has conclusively shown that in the trout embryo the progenitor (the manner of whose origin is unknown) of the definitive myofibrillae is a single, stout, deeply staining column, close to the nuclear wall externally, which undergoes a succession of radial and concentric longitudinal divisions. This observation would seem to dispose of the assumption of a direct mitochondrial origin of

[10] Heidenhain, 1913

myofibrillae in this form at least, in the manner of the current descriptions. And this conclusion is strengthened by the demonstration of mitochondria throughout the earlier development (Fig. 118).

Skeletal muscles develop from a portion of the mesodermic segments or primitive somites, called the *myotomes*. The *myoblasts* pass through the early histogenetic changes already described for cardiac muscle. In the frog, irritability was
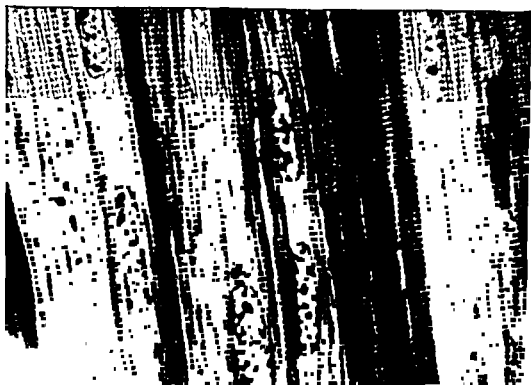
FIG. 123—LONGITUDINAL SECTION OF CROSS-STRIATED MUSCLE FROM THE TAIL OF FROG TADPOLE, SHOWING ALTERNATING DARK (*Q*) AND LIGHT (*J*) STRIPES, AND A NUMBER OF LONG OVAL NUCLEI. ×400

When this muscle is stretched in the resting condition, Z-membranes become visible, due to thickening following decrease of radial tension

shown by Hooker to follow closely upon differentiation of the fibrillae, and the establishment of nervous connections

The adult skeletal muscle fiber is a multinuclear structure. Is this condition the result of fusion of distinct myoblasts, or of growth of a single myoblast accompanied by nuclear proliferation? Both interpretations have been advanced; many observational data tend to show that a skeletal muscle fiber represents a myoblast which has elongated and multiplied its nuclei. In the trout embryo, however, considerable fusion of myoblasts occurs. The mode of nuclear division appears to be at first mitotic, and subsequently amitotic. In the tongue a small number of branched fibers have been described.

Striped muscle fibers differ in the relative amounts of myofibrillar and sarcoplasmic content. When the myofibrillae are relatively preponderant and the inter-

stitial granules sparse, the fiber is known as "light"; when the sarcoplasm, with its interstitial granules, is relatively abundant, "dark." In the latter fibers many of the nuclei may be centrally located. Most mammalian muscles contain both types of fibers, but with the light greatly in excess. When a muscle consists chiefly of
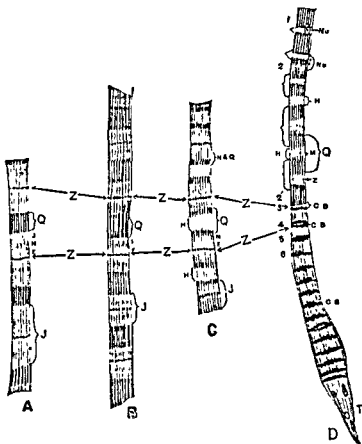
Fig 124—Four Successive Functional Stages of a Leg-muscle Fiber of the Sea Spider (Anoplodactylus Lentus)

Fiber *A* is in the relaxed condition, fibers *B*, *C*, and *D* in successively later phases of contraction Identical stages, in the same seriation, are met with when the four fibers are considered in a horizontal direction (between the telophragmata, *Z*), and when fiber *D* is considered in a vertical direction During contraction the deeply staining substance of the *Q*-disks of the relaxed fiber (*A*) divides and flows in opposite directions from the midline (mesophragma) toward the adjacent telophragmata (*B*) meanwhile involving the *N*-disks (*C*) and uniting about the telophragmata (*D*) to form the contraction bands (*CB*) of the contracted fiber. There occurs here a true reversal of striation as regards the deeply staining substance of *Q* during the formation of the contraction bands. The *H*-disk is a coincidence of contraction. Fiber *D* is stretched in its middle portion.

light fibers it is a white muscle; when the dark fibers are abundant it may be called red muscle. The former variety, for example the biceps muscle, acts more energetically but is more easily fatigued; the latter, like the muscles of mastication, respiration, the eyeball, and cardiac muscle, are functionally characterized by slower activity but less ready fatigue. The interstitial granules accordingly seem to be of nutritive significance. They are generally more abundant in the

J than in the Q segments. The J granules are of spherical form and smaller than the oval Q granules. Striped muscle fibers contain also a trophospongium (Holmgren), and a sparse perinuclear Golgi net. Adult muscle cannot regenerate, but is replaced by scar tissue. A young fiber is able to regenerate, the process involving
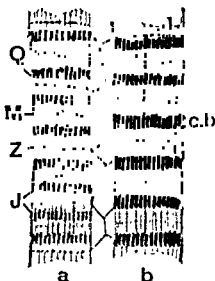

Fig. 125   Fig. 126.   Fig. 127.

Fig. 125.—Longitudinal Section of a Portion of a Striped Muscle Trabecula of Limulus, Showing a Nucleus of Serrated Contour with the Telophragmata Attached to the Serrations.

The nucleus lies in an undifferentiated mass of sarcoplasm containing below a deutoplasmic granule The adjacent myofibrils simulate a cell membrane. Fleming's fluid, iron-hematoxylin. ×2000.

Fig. 126.—Striated Fiber from a Leg Muscle of the Sea Spider (Anoplodactylus Lentus), Showing the Complexly Striped Condition Characteristic of Insect Muscle.

Q, anisotropic disk; J, isotropic disk; M, membrane of Heidenhain (mesophragma); Z, membrane of Krause (telophragma); H, median disk of Hensen; N, accessory disk of Englemann; E, terminal disk of Merkel ×1000

Fig 127.—Two Adjacent Muscle Fibers from Leg of Cockroach.

Fiber a is in the relaxed condition, fiber b in contracted condition. The resting fiber shows Q and J disks and M and Z-membrane, the contracted fiber is characterized by a succession of dark contraction bands (c. b) at the levels of the mesophragma. ×1350.

movement of proliferating nuclei toward the cut surface.[17] Muscle growth, as with exercise, depends upon enlargement of the muscle fiber, consequent upon a multiplication of fibrillae by process of longitudinal splitting, and their individual enlargement.
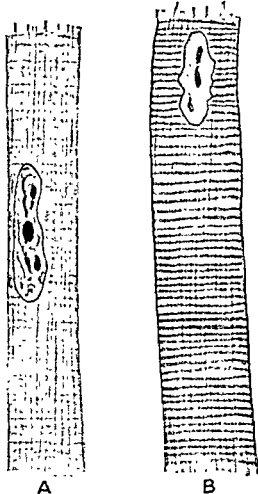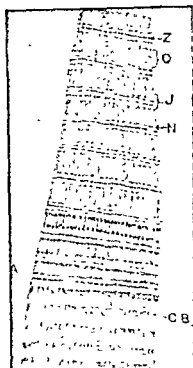
[17] Speidel, 1938.
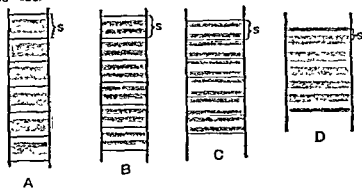
FIG. 128.

FIG. 129.

FIG 130.

FIG. 128.—FIBER FROM FROG'S GASTROCNEMIUS MUSCLE.

A, appearance of resting fiber teased in Ringer's solution, showing Q and J stripes and the Z-membrane. *B*, appearance of contracted fiber in same preparation, showing contraction bands. ×900.

FIG 129.—LONGITUDINAL SECTION OF PORTION OF LEG-MUSCLE FIBER OF A GRASSHOPPER.

The fiber passes abruptly from a condition of relaxation to one of contraction at point *A*, where a contraction band can be seen forming by process of fusion of opposite halves of two successive dark disks against the involved telophragma The telophragma is no longer discernible at the phase of contraction shown at *A*, due probably to its having become stretched by the horizontal tension at this level to a degree of delicacy beyond the limits of microscopic vision The formation of the contraction bands below *A* has effected a true reversal of striations as regards a deeply staining constituent of the dark disk. Flemming's fixation, iron-hematoxylin stain ×900

FIG. 130 (*A, B, C, D*).—DIAGRAMS ILLUSTRATING FOUR STAGES IN CONTRACTION OF A STRIPED MUSCLE FIBRIL.

J than in the Q segments. The J granules are of spherical form and smaller than the oval Q granules. Striped muscle fibers contain also a trophospongium (Holmgren), and a sparse perinuclear Golgi net. Adult muscle cannot regenerate, but is replaced by scar tissue. A young fiber is able to regenerate, the process involving

FIG. 125.   FIG 126   FIG. 127.

FIG. 125—LONGITUDINAL SECTION OF A PORTION OF A STRIPED MUSCLE TRABECULA OF LIMULUS, SHOWING A NUCLEUS OF SERRATED CONTOUR WITH THE TELOPHRAGMATA ATTACHED TO THE SERRATIONS.

The nucleus lies in an undifferentiated mass of sarcoplasm containing below a deutoplasmic granule. The adjacent myofibrils simulate a cell membrane. Fleming's fluid, iron-hematoxylin. ×2000.

FIG. 126.—STRIATED FIBER FROM A LEG MUSCLE OF THE SEA SPIDER (ANOPLODACTYLUS LENTUS), SHOWING THE COMPLEXLY STRIPED CONDITION CHARACTERISTIC OF INSECT MUSCLE.

Q, anisotropic disk; J, isotropic disk; M, membrane of Heidenhain (mesophragma); Z, membrane of Krause (telophragma); H, median disk of Hensen; N, accessory disk of Englemann; E, terminal disk of Merkel. ×1000

FIG. 127—TWO ADJACENT MUSCLE FIBERS FROM LEG OF COCKROACH.

Fiber a is in the relaxed condition, fiber b in contracted condition The resting fiber shows Q and J disks and M and Z-membrane, the contracted fiber is characterized by a succession of dark contraction bands (c. b) at the levels of the mesophragma. ×1350.

movement of proliferating nuclei toward the cut surface.[17] Muscle growth, as with exercise, depends upon enlargement of the muscle fiber, consequent upon a multiplication of fibrillae by process of longitudinal splitting, and their individual enlargement.

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[17] Speidel, 1938.

A   B

FIG. 128.   FIG. 129.

A   B   C   D

FIG. 130.

FIG 128—FIBER FROM FROG'S GASTROCNEMIUS MUSCLE.

A, appearance of resting fiber teased in Ringer's solution, showing Q and J stripes and the Z-membrane *B*, appearance of contracted fiber in same preparation, showing contraction bands ×900.

FIG. 129—LONGITUDINAL SECTION OF PORTION OF LEG-MUSCLE FIBER OF A GRASSHOPPER.

The fiber passes abruptly from a condition of relaxation to one of contraction at point *A*, where a contraction band can be seen forming by process of fusion of opposite halves of two successive dark disks against the involved telophragma. The telophragma is no longer discernible at the phase of contraction shown at *A*, due probably to its having become stretched by the horizontal tension at this level to a degree of delicacy beyond the limits of microscopic vision The formation of the contraction bands below *A* has effected a true reversal of striations as regards a deeply staining constituent of the dark disk. Flemming's fixation, iron-hematoxylin stain ×900

FIG. 130 (*A, B, C, D*).—DIAGRAMS ILLUSTRATING FOUR STAGES IN CONTRACTION OF A STRIPED MUSCLE FIBRIL.

MUSCULAR CONTRACTION

The explanation of striped muscle contraction which fits best the histologic data is one expressed in terms of surface tension phenomena in the constituent myofibrils of the striated fibers. It is obvious that no theory of muscle contraction can be adequate that is not based upon, and consistent with, the structural changes which the striped fibril undergoes during contraction. The primary histologic change concerns a reversal of striations as regards a dim and deeper staining substance of the Q disk, resulting in the formation of contraction bands, coincident with a shortening and thickening of the sarcomeres. The diagrams of Figure 130 are designed to illustrate these changes in a single contracting myofibril. The undivided Q disk of the resting fibril *A* is bisected at the beginning of contraction (*B*) by the appearance of an H disk. The resulting halves of the dividing Q disk move in opposite directions toward the terminal telophragmata of the respective sarcomeres (*C*) and fuse with similar opposite halves of successive Q disks to form the contraction bands of the contracted fiber (*D*). Meanwhile the constituent sarcomeres (*S*) have shortened and thickened, and the fibrils and fiber have contracted.

Macallum [18] and Menten [19] have shown that potassium salts, certain chlorides and phosphates are segregated in the dim disks; and Menten's illustrations indicate that these crystalloids (*electrolytes*) *change their position during contraction from the dim disk to the originally clear disk, that is from the Q disks to the contraction bands*. During contraction, therefore, there occurs a movement of electrolytes from the mesophragma to the terminal telophragmata of successive sarcomeres. The passage of these charged ions among the ultimate colloidal particles of the clear disks may be the fundamental factor in the production of shortened and thickened sarcomeres, coincident with the formation of contraction bands during contraction.

The details of this hypothesis, which involves the factor of surface tension, are illustrated in the diagrams *A* and *B* of Figure 131. In the resting fiber *A*, the black dots of the dim disks represent negatively charged ions, resulting from the passage of an electric current following the entrance of the nervous stimulus at the levels of the mesophragmata. The electrical current of action is assumed to pass from the mesophragma to the terminal telophragmata of the three sarcomeres through the agency of the ions. The ellipsoids of the clear disks represent positively charged ultimate colloidal particles of the essentially colloidal ooze of these areas.

Fig. 131 (*A* and *B*). — Diagrams Illustrating the Changes in the Physicochemical Constitution of the Striped Muscle Fibril during Contraction.

In the contracted fibril *B*, the electrolytes are shown massed at the levels of the telophragmata, that is, in the resulting contraction bands. In the passage of the negatively .... colloidal particles of the clear disk ....utralize their surfaces results in the ...les results in the increase of their surface tension and a consequent change of shape from ellipsoidal to spherical form. This change of shape of the ultimate colloidal particles constitutes the essence of striated muscle contraction. It may be assumed that when the nervous impulse

[18] Macallum, A. B., 1905.
[19] Menten, 1908.

ceases, the above-described process becomes reversed and the sarcomeres in consequence return to their original condition of equilibrium characteristic of the uncontracted fiber.

The above outlined hypothesis permits also a consistent interpretation of intercalated disks as irreversible contraction bands. The following facts may be rehearsed at this point: (1) the simplest forms of intercalated disks are such as are either bisected by a telophragma, bounded on only one surface by a telophragma or bounded on both surfaces by these membranes. (2) The primary type of intercalated disk is essentially similar to a contraction band. (3) Contraction bands are essentially double structures, consisting of
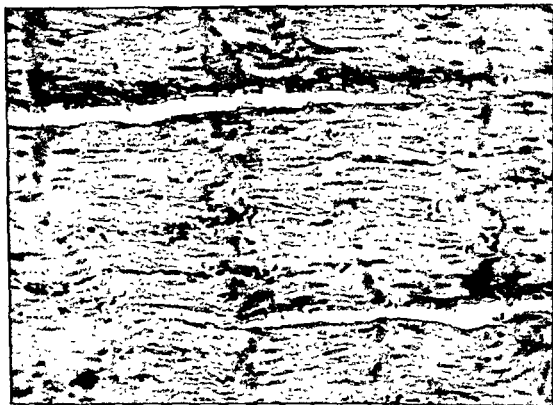
Fig 132.—Longitudinal Section of Several Columns of Contracting Smooth Muscle from the Gizzard of a Two-month-old Chicken, Showing Four Contraction Waves Composed of Horizontally Aligned Contraction Nodes on Adjacent Cells. ×266.

two relatively independent halves separated by a telophragma. (4) When striped muscle functions to the point of exhaustion there accumulates in the muscle a relatively excessive quantity of lactic acid. (5) Acid precipitates, that is, effects an irreversible coagulation of protoplasm

In the presence, therefore, of a relatively excessive amount of lactic acid during contraction, certain contraction bands may become irreversibly coagulated. Such would persist as intercalated disks, both in cardiac and skeletal muscle, of the type bisected by a telophragma. When one half of this compound contraction band remains capable of reversal while the other half has become irreversibly coagulated, there results a disk bounded on one side by a telophragma. When opposite halves of two adjacent contraction bands become incapable of reversal there results the third variety of simpler disk bounded on both borders by a telophragma, the middle area having become altered secondarily by the infiltration of interfiber tissue fluid so as to produce an apparently homogeneous intercalated disk of this variety.

Transitional Muscle.—This term has been applied to patches of smooth muscle in certain organs showing a variable condition of transverse striping. Such muscle has been

described in the gizzard of chickens, ducks and pigeons.[20] In alleged later and definitive stages it has been described also in the bladder of the young dog following the experimental induction of rhythmical contraction by means of the passage of a solution of
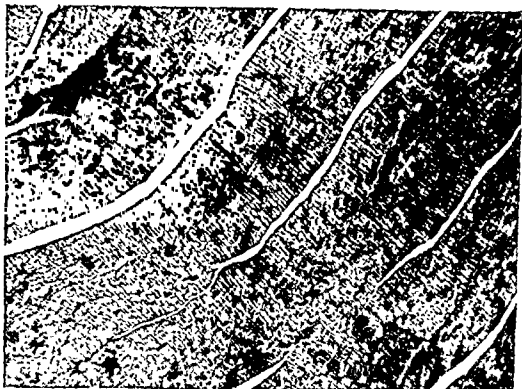
FIG. 133—LONGITUDINAL SECTION OF SEVERAL COLUMNS OF SMOOTH MUSCLE FROM THE GIZZARD OF TWO-MONTH-OLD CHICKEN, SHOWING A CONDITION SUGGESTIVE OF CROSS-STRIATED CARDIAC OR SKELETAL MUSCLE, THE RESULT OF A MECHANICAL DEFORMATION FOLLOWING CONTRACTION IN AN ADJACENT REGION. ×150

boric acid under gravity pressure.[21] The condition is characterized by the occurrence of an alternation of light and dark transverse bands of greatly varying width and a very variable degree of spacing. It has been interpreted as showing a transition between ordinary smooth muscle and genuine cross-striated muscle. The relatively wide dark bands are supposed to represent the Q bands of cross-striated muscle, the alternating lighter bands the J bands. Conditions of wide spacing of the bands (Fig. 132) are interpreted as showing earlier stages of transition; those of thinner more closely spaced bands (Fig. 133), the later stages of transition to cross-striated muscle. Structures comparable to ground (Z) membrane have not been designated.

FIG. 134—SEMIDIAGRAMMATIC ILLUSTRATION OF A COLLECTION OF SMOOTH MUSCLE CELLS FROM THE GIZZARD OF A CHICKEN (FIG. 133) PASSIVELY MODIFIED BY A LONGITUDINAL BUCKLING TO SIMULATE CROSS-STRIATIONS

In terms of this interpretation, the cross-striated structure of cardiac muscle is the result of rhythmical function rather than the antecedent morphologic mechanism sup-

20 Carey, 1936.
21 Carey, 1921.

porting such rhythmic contraction. However, the structure described as "transitional muscle" is simply smooth muscle in various degrees of contraction or in various degrees

FIG. 135.—LONGITUDINAL SECTION OF A SMOOTH MUSCLE CELL SHOWING ONE MEDIAN CONTRACTION NODE, FROM A CONTRACTION WAVE IN FIG. 137. ×900.

of distortion. Such muscle contains no stripes comparable to those of genuine cross-striated muscle. We are dealing simply with simulacra of cross-striated muscle. The bands are not genuine Q and J stripes. The wide dark bands are contraction nodes in fairly precise horizontal alignment on adjacent smooth muscle cells. The narrow and closely spaced bands which appear in certain areas of smooth muscle, simulating J and Q bands of cardiac and skeletal muscle, are simply undulating or zigzag distortions (Fig. 134). When blocks of tissue of chicken gizzard, stained sections from which showed a cross-striped condition, are dissociated in solutions of caustic potash discrete typical smooth muscle cells are readily obtained, some with variable numbers of contraction nodes, others with many gentle or sharp undulations and frequently showing terminal spiral twists (Fig. 136, B). Moreover, large areas of urinary bladder wall from young dogs show the same closely striped structure as in the case of bladders subjected to experimental rhythmical contraction (Fig 138). Similar areas may readily be found in sections of any portion of the smooth muscle wall of the alimentary canal

The following finding is especially illuminating as explaining the closely cross-striped appearance of certain specimens of smooth muscle: In a transverse section of the colon of the dog where the outer longitudinal smooth muscle layer was sharply contracted as shown by widely spaced contraction waves, large areas of the inner circular layer showed a condition of close cross-striping suggestive of cardiac muscle. On inspection with oil immersion lens typical fusiform smooth muscle cells could be seen in conditions of buckling, resembling accordion plaiting, giving a superficial appearance of genuine cross striation comprising Q and J disks In a section of the lower end of the esophagus of the cat, conditions were reversed; here the inner circular layer showed widely spaced contraction waves, and the adjacent area of the outer longitudinal layer showed a condition of close striation, and a corrugation of the constituent cells. Muscle transitional in structure between smooth muscle and cardiac muscle has not been demonstrated to exist.

The condition described as transitional muscle is merely smooth muscle distorted to simulate cross-striated muscle. Where the dark bands are relatively wide and widely
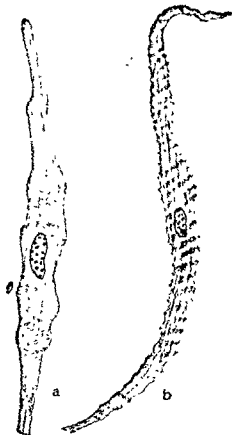
FIG 136.—SMOOTH MUSCLE CELLS.

a, Smooth muscle cell from gizzard of chicken (Fig. 132) showing a succession of contraction nodes; b, cell from same preparation in region of tendon junction (Fig. 133) showing a condition of cross-striping, the result of a mechanical distortion imposed by its location between a region of contracting muscle and an opposing inelastic barrier of connective tissue. ×900

spaced the condition signifies normal contraction nodes; where the bands are narrow and closely spaced we are dealing with a deformation of smooth muscle, the effect of a mechanical adjustment of fusiform cells to exiguous confines resulting from pressure of an area of contracting cells on one side against a connective tissue barrier on the opposite side.

We must now consider the muscle as a whole. For this purpose we may select any well-known muscle, for example, the biceps. A muscle as seen in transverse

FIG. 137.—TRANSVERSE SECTION OF COLON OF DOG, SHOWING SEVERAL IRREGULAR CONTRACTION WAVES IN THE CIRCULAR SMOOTH MUSCLE LAYER. ×170

section is enveloped in a moderately dense, fibro-elastic membrane, the *epimysium* (external perimysium); this gives off septa which separate the muscle into a larger or smaller number of bundles, depending upon its size, each bundle, or *fasciculus*, being again separately closely enveloped in a fibro-elastic covering, the *perimysium* (internal perimysium). Each fasciculus is, moreover, again subdivided into larger and smaller collections of muscle fibers, each bundle imperfectly separated from its fellows by septa from the perimysium, the *endomysium*. The ultimate subdivisions of the endomysium completely envelop each fiber and blend with the sarcolemma. This brings us to an individual fiber. Each fiber is inclosed in a sarcolemma. The myofibrillae are collected into larger and smaller bundles, *Kölliker's columns*, separated from each other by semifluid, granular sarcoplasm; these collections in cross-section are known as the *areas of Cohnheim*. They represent the definitive division products of the original group of fibrils (Heidenhain). The ultimate histologic units are the myofibrillae or sarcostyles. But these may

consist of still more delicate fibrils; in Limulus muscle, for example, the myofibrils may be resolved into successively finer fibrils to the limits of visibility.

Heart muscle can be similarly, but less precisely divided, the endocardium and epicardium corresponding to the epimysium. Fasciculi and perimysium are not so readily distinguished, but the endomysium is related to cardiac muscle in a manner essentially similar to that described for skeletal muscle.

FIG. 138.—AREA OF WALL OF NORMAL BLADDER OF YOUNG DOG, SHOWING PASSIVELY DISTORTED SMOOTH MUSCLE, SIMULATING CROSS-STRIATED MUSCLE. ×875.

The student should have well in hand the several criteria for the differentiation of the three types of muscle, both in transverse and longitudinal sections; and of smooth muscle from the dense white fibrous connective tissue. In brief, cross-sections of skeletal striped muscle can be readily distinguished on the basis of their greater diameter and the peripheral position of the nucleus. Both cardiac and smooth muscle fibers have a central nucleus and peripheral fibrillae; but the fibers of the cardiac muscle are more or less polygonal in outline and more constant in size, excepting occasional branches, while the smooth cells are circular in outline and of very diverse diameters, depending upon the different levels at which the section passes through adjacent fusiform cells. In longitudinal sections the cardiac muscle can be easily recognized by its branching character and the presence of intercalated disks; smooth muscle by the fusiform character of its associated cells. Smooth muscle is frequently difficult to distinguish from compact, white fibrous connective tissue. When both are present in the same section, stained with the

spaced the condition signifies normal contraction nodes; where the bands are narrow and closely spaced we are dealing with a deformation of smooth muscle, the effect of a mechanical adjustment of fusiform cells to exiguous confines resulting from *pressure of an area of contracting cells on one side against a connective tissue barrier on the opposite side.*

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WAVES IN THE CIRCULAR SMOOTH MUSCLE LAYER. ×170.

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FIG. 138—AREA OF WALL OF NORMAL BLADDER OF YOUNG DOG, SHOWING PASSIVELY DISTORTED SMOOTH MUSCLE, SIMULATING CROSS-STRIATED MUSCLE. ×875.

The student should have well in hand the several criteria for the differentiation of the three types of muscle, both in transverse and longitudinal sections; and of smooth muscle from the dense white fibrous connective tissue. In brief, cross-sections of skeletal striped muscle can be readily distinguished on the basis of their greater diameter and the peripheral position of the nucleus. Both cardiac and smooth muscle fibers have a central nucleus and peripheral fibrillae; but the fibers of the cardiac muscle are more or less polygonal in outline and more constant in size, excepting occasional branches, while the smooth cells are circular in outline and of very diverse diameters, depending upon the different levels at which the section passes through adjacent fusiform cells. In longitudinal sections the cardiac muscle can be easily recognized by its branching character and the presence of intercalated disks; smooth muscle by the fusiform character of its associated cells. Smooth muscle is frequently difficult to distinguish from compact, white fibrous connective tissue. When both are present in the same section, stained with the

FIG. 139—STRIATED MUSCLE FIBERS OF THE DOG.

The blood vessels have been filled by injection with a gelatinous mass and are represented in black. One whole fasciculus and one fiber from an adjacent fasciculus have been included. *a*, perimysium; *b*, endomysium; *c*, a large vein seen in transection. The section was not stained. ×53

routine hematoxylin-eosin technic, the two exhibit a slight difference in staining reaction. The smooth muscle commonly stains a deeper red; the collagenous fibers have a lighter orange tinge. Moreover, from a morphological standpoint, while portions of the white fibrous connective tissue may appear spindle-shaped, thus simulating the unit of smooth muscle structure, the associated nuclei of enveloping connective tissue cells are peripheral to the bundle, whereas the nucleus of smooth muscle is of course in the center of the analogous structure, the muscle cell.

FIG 140—STRIATED MUSCLE OF A CAT SEEN IN TRANSECTION.

The blood vessels have been injected and are black in the figure. At *a*, an artery is contracted and empty. The heavy black vessels are veins and arterioles; the small black dots are capillaries in transection. One whole fasciculus is represented and is surrounded by a delicate perimysium of connective tissue. Between the muscle fibers is the still more delicate endomysium. The larger vessels are almost exclusively found in the perimysium. The section was not stained. ×80.

BLOOD SUPPLY

The blood vessels of voluntary striped muscle distribute their larger trunks within the connective tissue of the epimysium. The smaller branches penetrate the endomysium and supply a rich capillary plexus with long rectangular meshes

(Fig. 139). The network of capillaries surrounds the muscle fibers so completely that each fiber is placed in relation with four or five capillary vessels which run parallel with the long axis of the fiber. Krogh [22] estimates that a transection of 0.5 millimeter in diameter contains about 700 parallel capillaries in relation to about 200 muscle fibers. He gives the number of capillaries per square millimeter of skeletal muscle in man as 2000. On the basis of a total muscle weight of 50 kilograms, he calculates that the total length of the capillaries in striped muscle would be 100,000 kilometers, two and one-half times the distance around the earth. The total surface area would be 6300 square meters. The blood supply of cardiac muscle is in general similar, but even more abundant and intimate, with respect to its terminal meshes. The blood supply of smooth muscle is considered to be relatively meager.

Numerous *lymphatics* occur in the perivascular connective tissue. These lymphatic vessels are especially abundant in cardiac muscle.

NERVE SUPPLY

Skeletal muscle is innervated both by cerebrospinal and sympathetic nerves, supported in the connective tissue envelopes and septa. The former include both sensory and motor fibers ending in *muscle spindles* and *motor end-organs* respectively. These endings will be further described in Chapter VI. The sympathetic or accessory fibers (Fig. 141)—relatively sparse and delicate, and in close relationship to the motor fibers and endings—terminate in special end-plates, close-meshed networks of generally oval outline Boeke [23] suggests that they mediate the maintenance of muscle tone.

FIG. 141.—MOTOR END-PLATE ON AN INTERCOSTAL MUSCLE FIBER OF A YOUNG RABBIT

The motor nerve fiber *m* is accompanied by an accessory (sympathetic) fiber, *af* (Boeke)

Cardiac muscle is supplied only with sympathetic motor fibers. These terminate on the muscle fibers in brushes of fibrils, but without highly specialized endings. Sensory fibrils from the vagus are distributed to the cardiac endomysium. Each smooth muscle cell, likewise, is supplied with a sympathetic fibril, ending in minute knobs or plates

According to Malone, [24] the three types of muscle are innervated by three histologically distinct types of nerve cells, representing specific functional differences. The cells supplying heart muscle are from the standpoint of size and granular (chromophilic) content, intermediate between those supplying smooth and those supplying skeletal striped muscle. (See Fig. 150.)

[22] Krogh, 1922
[23] Boeke, 1913
[24] Malone, 1913

FIG. 139.—STRIATED MUSCLE FIBERS OF THE DOG.

The blood vessels have been filled by injection with a gelatinous mass and are represented in black. One whole fasciculus and one fiber from an adjacent fasciculus have been included. *a*, perimysium; *b*, endomysium; *c*, a large vein seen in transection. The section was not stained ×53.

routine hematoxylin-eosin technic, the two exhibit a slight difference in staining reaction. The smooth muscle commonly stains a deeper red; the collagenous fibers have a lighter orange tinge. Moreover, from a morphological standpoint, while portions of the white fibrous connective tissue may appear spindle-shaped, thus simulating the unit of smooth muscle structure, the associated nuclei of enveloping connective tissue cells are peripheral to the bundle, whereas the nucleus of smooth muscle is of course in the center of the analogous structure, the muscle cell.

FIG 140.—STRIATED MUSCLE OF A CAT SEEN IN TRANSECTION.

The blood vessels have been injected and are black in the figure. At *a*, an artery is contracted and empty. The heavy black vessels are veins and arterioles; the small black dots are capillaries in transection. One whole fasciculus is represented and is surrounded by a delicate perimysium of connective tissue. Between the muscle fibers is the still more delicate endomysium. The larger vessels are almost exclusively found in the perimysium. The section was not stained. ×80.

BLOOD SUPPLY

The blood vessels of voluntary striped muscle distribute their larger trunks within the connective tissue of the epimysium. The smaller branches penetrate the endomysium and supply a rich capillary plexus with long rectangular meshes

division. According to Loevy the fibrils are developed from fibroblasts; the definitive tendon cells, which bound the primary bundles, arise from cells of Ranvier. Both come from mesenchymal cells, but the fibroblasts entirely disappear, while the cells of Ranvier persist as the characteristic winged *tendon cells*.

Ligaments, fascia and *aponeuroses* are very similar to tendon, but are less compact and contain more elastic tissue.

Bursae are epithelium-lined sacs in connection with the large diarthroses and certain locations where tendons are subject to friction.

FIG 143

FIG. 144.

FIG 143—TRANSVERSE SECTION OF TENDON OF TAIL OF ADULT MOUSE.

It consists of four secondary bundles or fasciculi, *s b* ; *f b.*, primary bundle; *p.*, epitendineum; *c.R* , tendon cell (cell of Ranvier). (After Loevy, *Anat. Anz.*, 1913, 45:10.)

FIG. 144—END OF MUSCLE FIBER FROM HUMAN TONGUE.

Showing the direct continuity between myofibrils and tendon fibrils through the terminal sarcolemma. ×700. (After J. Sobotta, *Ztschr. mkr. anat. Forsch.*, 1924, 1:2.)

Tendons are supplied with blood vessels and sensory nerve endings, in a manner very similar to skeletal muscle.

The exact manner of the attachment of striped muscle to tendon is still disputed. According to certain investigators,[26] the myofibrils and tendon fibrils are directly continuous through the sarcolemma. Others[27] hold that the muscle ends sharply, remaining striped to its termination, and that the rounded or pointed end is completely enveloped by the sarcolemma. The muscle fibers are described as being dovetailed into the tendon, the tendon fibrils being attached to the sarcolemma. This is the more commonly accepted interpretation; but it seems probable that both types of muscle-tendon connections occur in different muscles, for in certain muscles the cross-striations become gradually more vague toward the ten-

[26] Schultze, 1912
[27] Baldwin, 1912.

TENDONS

A tendon, taken as a whole, is invested by a dense fibro-elastic membrane, the epitendineum, or *vagina fibrosa*. Where tendons play in bony grooves this may be modified into a tendon sheath, the epitendineum acquiring a mucous cavity, when it becomes known as a *vagina mucosa*. Septa from the epitendineum penetrate the mass and divide the tendon imperfectly into irregular columns, the tertiary bundles.
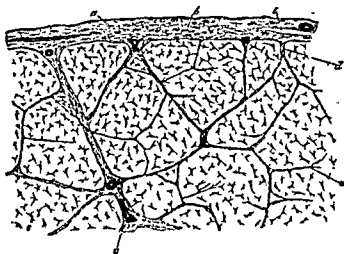
FIG. 142.—PORTION OF A TRANSECTION OF A LARGE TENDON.

a, fibrous capsule with circular, and at *b*, longitudinal bundles of connective tissue; *c*, *d*, and *e*, fibrous septa between the fasciculi of the tendon; *l*, lymphatic cleft. Moderately magnified. (Shafer.)

These are further divisible into more regular aggregations of fibrils, completely enveloped by a peritendineum, which are the *tendon fasciculi*. These correspond to the muscle fasciculi enveloped by perimysium. In the mouse, tendons consist of from 1 to 11 fasciculi; in the chick from 2 to 5.[28] Each fasciculus consists of elementary bundles of collagenous fibrils, enveloped by a complete sheath formed by the anastomosing processes of the tendon cells (cells of Ranvier). The cell bodies lie between these *primary bundles;* they are connected to each other by their processes, forming an endothelial tube (Ranvier), the cells of which have a characteristic mesothelial appearance in silver nitrate preparations.

In the tendons of the tail of the mouse, Loevy describes the cells as flat, rectangular, and rhomboidal; they are parallel to the long axis of the tendon, two of their surfaces extended into flat plates or wings which effect a union with "wings" of adjacent cells A cell may have from 2 to 4 wings. The wings or plates have been interpreted as elastic in nature, but do not react to specific stains for elastic tissue. Each cell contains a spherical or oval deeply staining nucleus. The nuclei of pairs of cells are so placed as to be immediately adjacent, the result of cell

[28] Loevy, 1913

division. According to Loevy the fibrils are developed from fibroblasts; the definitive tendon cells, which bound the primary bundles, arise from cells of Ranvier. Both come from mesenchymal cells, but the fibroblasts entirely disappear, while the cells of Ranvier persist as the characteristic winged *tendon cells*.

Ligaments, fascia and *aponeuroses* are very similar to tendon, but are less compact and contain more elastic tissue.

Bursae are epithelium-lined sacs in connection with the large diarthroses and certain locations where tendons are subject to friction.

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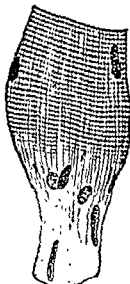
FIG 144—END OF MUSCLE FIBER FROM HUMAN TONGUE.

Showing the direct continuity between myofibrils and tendon fibrils through the terminal sarcolemma. ×700. (After J. Sobotta, *Ztschr. mikr anat. Forsch.*, 1924, 1 2.)

Tendons are supplied with blood vessels and sensory nerve endings, in a manner very similar to skeletal muscle.

The exact manner of the attachment of striped muscle to tendon is still disputed. According to certain investigators,[26] the myofibrils and tendon fibrils are directly continuous through the sarcolemma. Others[27] hold that the muscle ends sharply, remaining striped to its termination, and that the rounded or pointed end is completely enveloped by the sarcolemma. The muscle fibers are described as being dovetailed into the tendon, the tendon fibrils being attached to the sarcolemma. This is the more commonly accepted interpretation; but it seems probable that both types of muscle-tendon connections occur in different muscles, for in certain muscles the cross-striations become gradually more vague toward the ten-

[26] Schultze, 1912.

[27] Baldwin, 1912.

don, and the region of transition from muscle to tendon is by no means sharply marked (Fig. 144). Moreover, the fact that certain ligaments and aponeuroses arise normally by transformation of muscle adds support to the idea of muscle-tendon continuity.

Baldwin distinguishes two general types of muscle termination with respect to tendon: one in which the long axes of tendon and muscle fiber coincide; a second in which they meet at an angle. In neither type does he recognize a direct continuity between muscle and tendon fibrils. In the first type the sarcolemma is said to present pointed ends, to which the tendon fibrils are attached; in the second, the sarcolemma presents a flat surface which rests directly against the attached structure, whether fascia, periosteum, or ligaments. Carr,[28] on the basis of his investigation of the muscle-tendon attachment in the striated muscle of the fetal pig, concludes that the chief connection between muscle fiber and tendon is by means of myofibrils which continue into tendon fibrils at the end of the muscle fiber whether the muscle attaches to the tendon obliquely or rectilinearly. Lymphatics are abundant in tendons.

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[28] Carr, 1931.

CHAPTER V

NERVOUS TISSUE

Nervous tissue comprises nerve cells, nerve fibers and supporting neuroglia. In the protoplasm of nervous tissue proper (neuroplasm) the fundamental properties of irritability and conductivity have become predominant. The nervous system includes the cerebrospinal—comprising the central (brain and spinal cord) and the peripheral (cerebral and spinal nerves) portions—and the sympathetic divisions. For convenience we may speak also of the central and peripheral nervous systems, the latter including the sympathetic division. The essential unit of structure, comparable to the cell of other tissues, is here the neuron, or neurocyte. A *neuron* is a nerve cell in the broadest sense of the term. It consists of the *cell body* (nerve cell of the older writers, cyton), together with all of its processes. These latter are divisible into two varieties. the *axon* and the *dendrons (dendrites)*.

The neurons are among the largest cells of the body. Their cell body is of variable size, in some cases extremely minute, at other times sufficiently large to be readily observed with the unaided eye. Their processes, usually of considerable number, vary in length from a millimeter or less, up to half the height of man. It is therefore obviously impossible to study microscopically at one time the entire course of these longer processes. This circumstance renders it advisable to retain the term *nerve fiber* of the older writers to designate, not as was the former conception, a histological entity, but rather that portion of those long processes of the nerve cell which pursues its course, as a rule, outside of the gray matter of the central portion of the cerebrospinal division.

On this basis we may divide the neuron into the nerve cell and the nerve fiber. The former term includes the cell body, or cyton, with its dendrons and the proximal portion of its axon; the distal portion of the axon forming the essential part of a long nerve fiber. The nerve cells are found throughout the gray matter of the central portion and in the peripheral ganglia of the cerebrospinal division and in the sympathetic ganglia. Nerve fibers occur in the white matter of the central portion and in the nerve trunks and ganglia of the peripheral portions of the nervous system.

In the peripheral nervous system the nervous tissues are chiefly supported by the connective tissues, but in the central portion a special form of supporting tissue, the *neuroglia,* is also found. This is described below.

FIG. 145.—DIAGRAM OF A NEURON.

a.h., axon hillock; *a.x.*, axon, *c.*, cytoplasm, the Nissl granules have been stained; *d*, dendrons, *m.*, myelin sheath of the nerve fiber; *m'*, muscle fiber; *n*, nucleus, *n'*, nucleolus, *n of n*, nucleus of the neurilemma of the nerve fiber, *n R*, node of Ranvier; *s f*, collateral, *s L*, segment of Lantermann; *tel.*, telodendrion or terminal arborization which here forms a motor end-plate. (Barker.)

THE NERVE CELL

(*Cyton, Cell Body, Perikaryon, Ganglion Cell*)

This term, as already stated, includes the cell body with its dendrons and the proximal portion of its long axon. The cell bodies vary in size from 4 μ to 200 μ in diameter. Their shape is chiefly dependent upon the number of their dendritic processes. Unipolar nerve cells, with but a single process, are flask-shaped or pyriform; bipolar cells, whose processes are usually derived from opposite extremities, are most frequently fusiform; multipolar nerve cells, from the considerable number of their processes, are irregularly stellate.

Nucleus.—The cytoplasm of the cell is finely granular and contains a large vesicular nucleus which, as a rule, is excentrically situated. The appearance of this large nucleus is quite characteristic of the nerve cell as distinguished from the cells of other tissue. The nuclear membrane is distinct and highly chromatic. The content of the nucleus, however, except for the large spherical nucleolus which is quite constantly present, is noticeably deficient in chromatin. Those few small karyosomes which are present are mostly adherent to the inner surface of the nuclear membrane. The achromatic nucleoplasm forms the greater portion of the nucleus. Occasionally the chromatin forms still finer granules, and is more equally distributed throughout the nucleus.

Cytoplasm.—The finer structure of the cytoplasm of the nerve cell is the subject of considerable difference of opinion. The studies of Nissl have shown that *it is divisible into a substance which is readily stained by methylene blue, thionin, etc.* (the stainable substance of Nissl, tigroid of von Lenhossék), and an apparently homogeneous substance which is not so readily stained (the unstainable substance of Nissl).

Nissl's substance, chromophilic or *tigroid substance,* occurs in the form of flake-like granules of varying size and irregular shape. Their disposition within the cytoplasm is subject to considerable variations in different nerve cells, but according to Nissl it is fairly constant in cells of the same location for any given species. The amount also of the chromophilic substance is subject to variation depending upon the functional condition of the individual. It has been shown that the substance is greatly diminished by fatigue [1] and after surgical shock.[2] However, on the basis of a long series of carefully controlled experiments with dogs, cats, pigeons, sparrows, frogs and rats, Kocher concludes that the histologic structure of the nerve cell following activity shows no constant deviation from that of the corresponding resting cells of the controls. No deviation from the normal was evident even in cases of the most advanced fatigue.[3] Explanation of these contradictory results awaits further research. In general also, the longer the axon the greater the amount of chromophilic substance. Chemically, it is a nucleoprotein. There is considerable histologic evidence to indicate that it has a nuclear origin, appearing first in the form of chromidia, and it is accordingly sometimes designated as *cytochromatin.* Muhlmann [4] has shown, however, that tigroid nuclein is soluble in weak soda solutions while nucleus nuclein is not. It has been suggested (Heidenhain) that it may perhaps have an accessory nuclear function. According to Held it is present as a diffuse continuous substance, coagulated in the form of flakes and granules in fixed tissues. It is not discernible in the living cell. Study of neurocytes with the freezing-drying method of Bensley has revealed that the Nissl substance is actually discontinuous and actually segregated in the form of definite groups.[5]

FIG 146.—A UNIPOLAR GANGLION CELL OF A FROG.

a, cell body; *b,* axon; *c,* dendron. Methylene blue. Highly magnified. (von Smirnow)

Those nerve cells in which the Nissl substance is abundant are said to be in a *pyknomorphous,* those in which it is scanty in an *apyknomorphous* condition. The Nissl granules are apparently used up during functional activity of the nerve cell.

[1] Dolly, 1914.
[2] Crile, 1914.
[3] Kocher, 1916
[4] Muhlmann, 1929
[5] Bensley, R. R and Gersh, 1933.

The brain cells show a strong affinity for adrenalin, the secretion of the medulla of the suprarenal glands; this fact leads Crile (1914) to suspect that the Nissl substance is a volatile, unstable combination of certain elements of the brain cells and adrenalin because the suprarenal glands alone do not take the Nissl stain, and the brain deprived of adrenalin does not take Nissl stain.
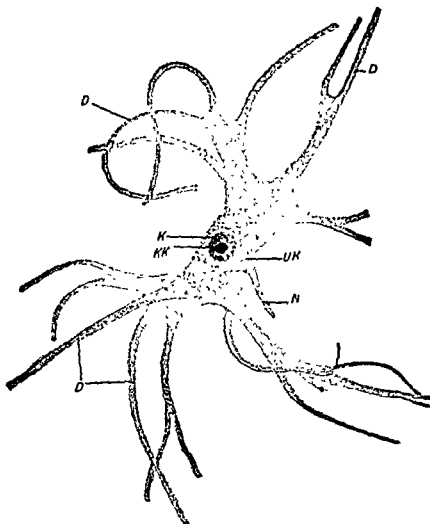
Fig. 147.—Isolated Motor Neuron from Ventral Horn of Spinal Cord of Calf. D, dendron; N, axon; UK, axon hillock; K, nucleus; KK, nucleolus ×160 (Schaffer.)

Nissl substance disappears in case of lesion of the neuron, but reappears in abundance after temporary injury and recovery of the cell. Such disappearance after section of the axon (axonal reaction) is accompanied by a swelling of the neuroplasm and the peripheral migration of the nucleus, after from ten to fifteen days.

Concerning the finer structure of the unstainable substance of Nissl, comparatively little is known. With varying methods of fixation this portion of the cytoplasm has been found to show very fine fibrils (neurofibrils), (Schultze,

Flemming, Apáthy, Bethe) and fine acidophil granules (neurosomes of Held; probably mitochondria). Besides these structures there remains a homogeneous ground substance or hyaloplasm, which, though of extreme physiological importance, in the usual histological preparations presents no structure. Centrosomes
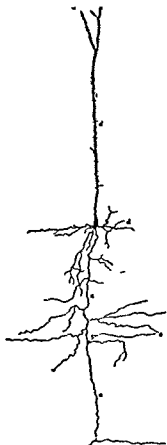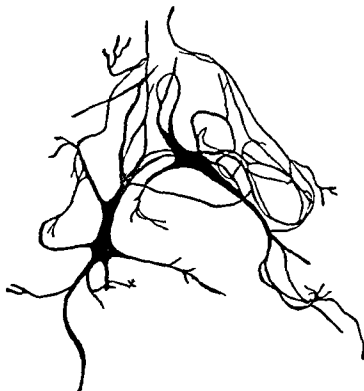
FIG. 148.   FIG. 149

FIG. 148—PYRAMIDAL MULTIPOLAR NERVE CELL FROM THE CEREBRAL CORTEX OF A MOUSE.
a, axon; *d*, dendrons; *c*, collaterals. Golgi technic. (Barker, after Ramon y Cajal.

FIG. 149—ISOLATED NERVE CELLS FROM THE SPINAL CORD OF MAN.
x, axon. Carmine. ×160 (Sobotta.)

and attraction spheres have been frequently observed in the nerve cells of the lower vertebrates, and occasionally in those of mammals.

The cytoplasm of many nerve cells contains a characteristic brownish-yellow *pigment*, whose fine granules have a tendency to accumulate in the vicinity of the nucleus.

Mitochondria also have been reported in ganglion cells of the rabbit.[6] Cowdry [7] describes granular and rod-like mitochondria in the spinal ganglion cells of a number of vertebrates, including man. They are said to occur throughout the entire neuron, axon as well as dendrons. They are regarded as fundamental constituents

[6] Schirokogoroff, 1913
[7] Cowdry, 1914

of the neuroplasm. It is suggested that they are concerned with the metabolism of the neurocyte.

Neurons are incapable of division; destroyed neurons cannot be replaced; the axon, however, may regenerate.

FIG. 150.—THREE TYPES OF NERVE CELLS SUPPLYING RESPECTIVELY CARDIAC (*1*), SMOOTH (*2*) AND (*3*) STRIATED MUSCLE

The cells supplying heart muscle are histologically intermediate between those supplying smooth and those supplying voluntary striated muscle; *1*, cells from nucleus cardiacus nervi vagi of lemur; *2*, cells from vagus sympathetic nucleus of lemur. X380. (After Malone, *Am. J. Anat.*, 1913, 15·1)

End-fibrils of other neurons have been demonstrated within the cytoplasm of the nerve cell. Apáthy has likewise demonstrated that fibrils occasionally pass from one neuron to another, so that we no longer consider that a neuron, though a

structural unit, is in all cases anatomically independent of all other neurons. The present status of this much discussed question seems to be comparable to that of the cell, as a histological unit of structure, which though formerly thought to exist independently of other cell units, has since been found to be frequently connected, as by the intercellular bridges of epithelium and of smooth muscle. The neurons of the nervous system, therefore, while being usually related to one another by contiguity or by contact only, may occasionally be more directly connected by
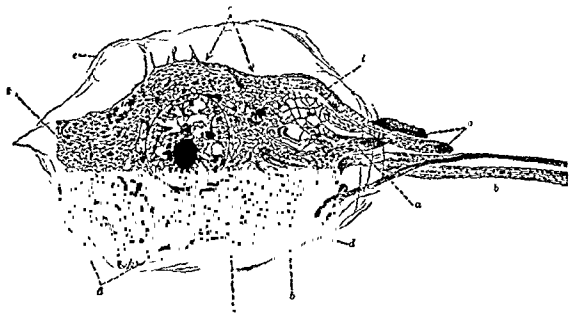
FIG. 151.—A NERVE CELL FROM THE TRAPEZOID NUCLEUS IN THE MIDBRAIN OF A RABBIT.

a, axon, *b*, axons of other nerve cells which terminate in relation and apparently fuse with the cytoplasm of the cell body; *c*, points of fusion or zones of concrescence; *d*, dendrons which have been cut off close to the cell body, *e*, neuroglia. The cytoplasm shows a neurofibrillar network and Nissl granules. Iron hematoxylin. Very highly magnified. (Held.)

fibrillae, which pass from the processes of one neuron to the cell body or processes of a second neuron (Apáthy, Bethe), or by "concrescence," as described by Held.

The nerve cells are surrounded by a narrow interval which separates them from the surrounding tissue. This is presumably a lymphatic or tissue fluid space. Holmgren has demonstrated also the presence, within the cytoplasm of the nerve cell, of minute canaliculi which form an intracellular network, more abundant near the surface of the cell, and which he has termed juice canaliculi, or trophospongium. These canaliculi may possibly account for the peculiar intracellular network which Golgi has demonstrated in the periphery of the nerve cell, by a modification of his rapid silver impregnation method.

The processes of the nerve cell are of two varieties: the one, broad, granular, and rapidly dividing in the vicinity of the cell body into a number of branching subdivisions, is the *dendron;* the other, long, slender, and finely but distinctly fibrillar, arises from the cell body direct, or from the base of a dendron, and passing for a considerable distance from the cell body, finally enters the nerve

of the neuroplasm. It is suggested that they are concerned with the metabolism of the neurocyte.

Neurons are incapable of division; destroyed neurons cannot be replaced; the axon, however, may regenerate.

FIG. 150—THREE TYPES OF NERVE CELLS SUPPLYING RESPECTIVELY CARDIAC (1), SMOOTH (2) AND (3) STRIATED MUSCLE

The cells supplying heart muscle are histologically intermediate between those supplying smooth and those supplying voluntary striated muscle; 1, cells from nucleus cardiacus nervi vagi of lemur; 2 cells from vagus sympathetic nucleus of lemur. ×580. (After Malone, *Am. J. Anat.*, 1913, 15:1.)

End-fibrils of other neurons have been demonstrated within the cytoplasm of the nerve cell. Apáthy has likewise demonstrated that fibrils occasionally pass from one neuron to another, so that we no longer consider that a neuron, though a

due to the clustering along their borders of minute lateral projections, the *gemmules.*

The terminal filaments of the dendronic arborization are frequently in relation with the cell bodies or axons of other neurons. This is called a *synapse.*
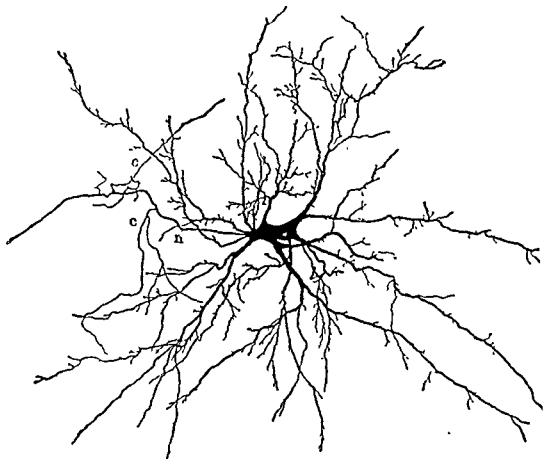
FIG. 154.—GOLGI CELL, TYPE I.
c, collaterals; *n,* axon Golgi's Stain. (Kölliker.)

Dendrons are *cellulipetal* or *afferent processes,* transmitting impulses to the cyton.

The Axon (*Neuraxis, Neuraxon, Neurite, Axis Cylinder Process*).—This process, in contradistinction to the dendron, is long and slender, as a rule does not arborize near its parent cell body, is of smooth and regular contour in Golgi preparations, and contains no chromophilic substance. It arises from the cell body, or less frequently from the base of a dendron, by a conical, clear area, the *axon hillock* or *implantation cone,* which, like the process itself, is devoid of chromophilic granules. It consists of a bundle of delicate neurofibrils '(axon fibrils) embedded in *axoplasm.* During early developmental stages the fibrils increase in number by a splitting of preëxisting fibrils.

At some little distance from the parent cell body the axon gives off very fine lateral branches, the *collaterals,* which leave the parent stem at the nodes of Ranvier at nearly right angles. These delicate branches, as also the axon proper,

fiber as its axis cylinder, or terminates in relation to some distant nerve cell. This latter process is the *axon*. Each cell body usually possesses a single axon and several dendrons. Cells without an axon are found in the retina and in the olfactory bulb; except for these, all nerve cells in the body of man possess an axon and usually but one such process. The subdivision of nerve cells into uni-, bi-, and multi-polar cells is chiefly based upon the number of their dendrons.

Dendrons (*Dendrites, Protoplasmic Processes*).—The dendrons of a nerve cell vary from one to a considerable number. They arise from the cell body by a broad stem, and quickly break into branches which can be traced for

Fig. 153.—INTRACELLULAR CANALICULI (TROPHOSPONGIUM OF HOLMGREN) WITHIN A SPINAL GANGLION CELL. (Holmgren.)
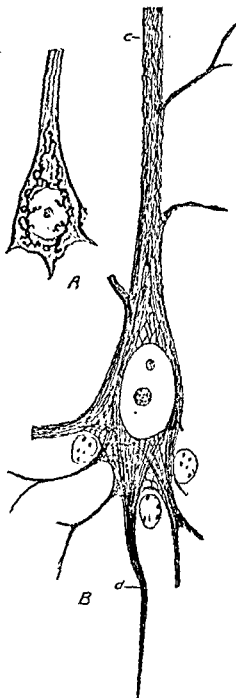
FIG. 152.—PYRAMIDAL NEURONS FROM CEREBRAL CORTEX OF RABBIT.

A, cell showing internal reticular apparatus of Golgi *B*, showing neurofibrils. *d*, axon. Silver nitrate method for neurofibrils. (Cajal.)

a considerable distance—in fact, the arborization of the dendrons is usually so extensive that it can be followed for only a short portion of its course. Occasionally dendrons do not branch until they have arrived at a considerable distance from their parent cell body.

The structure of the dendron is, to all appearances, similar to that of the cell body. The chromophilic substance is continued for some distance into the arborizing dendrons, which often possess a finely fibrillar appearance. In Golgi-stained preparations the dendrons frequently present a thorny appearance,

The cells of Type I possess a long axon which passes beyond the confines of the gray matter in which it arises and usually becomes the axis cylinder of a nerve fiber.

The cells of Type II possess a short axon which forms its terminal arborization in the vicinity of its parent cell body. The cells of this type are usually *association* and *commissural neurons;* they place in conduction relation other not very remote neurons. The cells of Type I, on the other hand, are more frequently *projection* neurons; they are distributed from the nerve centers to other and perhaps very different tissues, their courses lying in the long projection tracts and nerve trunks of the nervous system.

The cells of Type II are therefore most frequently intrinsic or endogenous neurons, their whole course lying in one division of the central nervous system, *e.g.,* the gray matter of the spinal cord. The cells of Type I are more frequently extrinsic or exogenous; they arise in one part of the nervous system to be distributed to a distant portion, *e.g.,* they arise in the peripheral ganglia and enter the spinal cord to terminate in its gray matter, or *vice versa.*

The size of a nerve cell is thought to bear a general relation to the length of its axon, the larger cells possessing the longer axons. The cells of Golgi's Type I are therefore larger than those of Type II. Likewise the cells of the motor tracts, whose axons are as a rule much longer than those of the sensory tracts, are characterized by their large size as compared with the sensory cells.

THE NERVE FIBER

The origin of the nerve fiber and its relation to the other portions of the neuron will be appreciated by tracing the course of the axon of a motor nerve cell of the ventral horn of gray matter in the spinal cord. This process, arising in the central gray matter, is at first a naked axon. It soon leaves the gray matter to traverse the white matter and makes its exit from the spinal cord as the axis cylinder of one of the fibers of a ventral nerve root. On leaving the gray matter the axon acquires a cylindrical sheath of myelin substance, the *medullary sheath, myelin sheath,* or *white substance of Schwann.*

On entering the ventral nerve root, which lies outside of the white matter of the spinal cord, the axon receives an epithelioid membranous sheath, the *neurilemma* or *nucleated sheath of Schwann.* The axon retains these two sheaths until near its termination, when the sheaths suddenly stop, the axon becoming again naked as it breaks into terminal fibrils.

Not all nerve fibers are medullated, nor do they all possess a neurilemma. The axons of the central nervous system are not supplied with a neurilemma until they pierce the meninges to enter the nerve roots. Those of the gray matter also have no appreciable medullary sheath. The axons of the peripheral nerve trunks and ganglia are all supplied with a neurilemma except at their terminals, as already explained. Yet some of the peripheral axons have a medullary sheath, while others have none. An axon with its enveloping sheaths constitutes a nerve

finally terminate by a sudden *end arborization*, or *telodendrion*, by which each axon is placed in relation with a large number of neurons, or a considerable area of surface. The telodendrion may terminate in minute knobs or plates, the *neuropodia.* The telodendrion is structurally apparently an efficient mechanism for mediating the phenomenon of axon reflex (Langley). The parent stem of the

FIG. 155—GOLGI NERVE CELL, TYPE II.
a, axon; *x*, dendron. (Kolliker.)

axon may be finally exhausted in its collaterals, or it may in turn end in a terminal arborization. Collaterals are said to be more frequent in the proximal than in the distal portion of the axon. The axon transmits impulses away from the cell body; it is a *cellulifugal* or efferent process.

According to the length of their axons, neurons are divided by Golgi into two types: Golgi cells, Type I (Deiters' cells) and Golgi cells, Type II (Golgi's cells).

The cells of Type I possess a long axon which passes beyond the confines of the gray matter in which it arises and usually becomes the axis cylinder of a nerve fiber.

The cells of Type II possess a short axon which forms its terminal arborization in the vicinity of its parent cell body. The cells of this type are usually *association* and *commissural neurons;* they place in conduction relation other not very remote neurons. The cells of Type I, on the other hand, are more frequently *projection* neurons; they are distributed from the nerve centers to other and perhaps very different tissues, their courses lying in the long projection tracts and nerve trunks of the nervous system.

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On entering the ventral nerve root, which lies outside of the white matter of the spinal cord, the axon receives an epithelioid membranous sheath, the *neurilemma* or *nucleated sheath of Schwann.* The axon retains these two sheaths until near its termination, when the sheaths suddenly stop, the axon becoming again naked as it breaks into terminal fibrils.

Not all nerve fibers are medullated, nor do they all possess a neurilemma. The axons of the central nervous system are not supplied with a neurilemma until they pierce the meninges to enter the nerve roots. Those of the gray matter also have no appreciable medullary sheath. The axons of the peripheral nerve trunks and ganglia are all supplied with a neurilemma except at their terminals, as already explained. Yet some of the peripheral axons have a medullary sheath, while others have none. An axon with its enveloping sheaths constitutes a nerve

finally terminate by a sudden *end arborization*, or *telodendrion*, by which each axon is placed in relation with a large number of neurons, or a considerable area of surface. The telodendrion may terminate in minute knobs or plates, the *neuropodia*. The telodendrion is structurally apparently an efficient mechanism for mediating the phenomenon of axon reflex (Langley). The parent stem of the

FIG. 155—GOLGI NERVE CELL, TYPE II.

a, axon; *x*, dendron. (Kölliker.)

axon may be finally exhausted in its collaterals, or it may in turn end in a terminal arborization. Collaterals are said to be more frequent in the proximal than in the distal portion of the axon. The axon transmits impulses away from the cell body; it is a *cellulifugal* or efferent process.

According to the length of their axons, neurons are divided by Golgi into two types: Golgi cells, Type I (Deiters' cells) and Golgi cells, Type II (Golgi's cells).

maximum effect of stimulation favors the view that the neuroplasm is the essential conducting substance.

Tashiro[9] has demonstrated that a living nerve gives off a definite amount of carbon dioxide, and that when the nerve is stimulated the amount of carbon dioxide production is increased. He conceives of the propagation of nerve impulses as a chemical change, the propagation being in essence a restoration of equilibrium in the nerve fiber disturbed at the point of contact.

The axis cylinder is, under certain conditions at least, found to be inclosed by an extremely delicate membrane, the *axolemma* of Kühne. The existence of this membrane as an integral part of a living axis cylinder has been denied by others. It may be simply a fixation artifact.

The Myelin Sheath (White Substance of Schwann, Medullary Sheath).—The myelin sheath forms a cylindrical investment for the axis cylinder. Medullated fibers vary greatly in diameter according to the amount of myelin present. It appears to be retained in position by the neurilemma, for when the latter is ruptured the myelin exudes in the form of myelin drops. The *myelin* thus obtained possesses the physical properties of a fat. It is also capable of being blackened by osmium tetroxide. By extraction with ether the myelin can be removed, leaving behind a supporting framework of *neurokeratin*. The function of myelin is probably nutritive, though it has been regarded as an insulating substance. It is thought to be present in small amounts even in so-called amyelinated fibers. It seems reasonable to suppose that it may have a double function, that is, nutritive and in part insulating

At frequent intervals in the course of the nerve fiber its myelin sheath suffers complete interruption, thus forming the annular constrictions or *nodes of Ranvier*. At these points the neurilemma dips in until it is in contact with the axis cylinder. Both the axis cylinder and the neurilemma are continued past the node without interruption.

The successive nodes of Ranvier divide the nerve fiber into *internodal segments*. Within each internodal segment the myelin sheath, on blackening with osmium tetroxide, presents clear intervals which penetrate the myelin in such manner as to give the appearance of obliquely disposed clear lines or incisions. These *incisures of Schmidt* (Schmidt-Lantermann lines) have not been satisfactorily explained and cannot be demonstrated in the intact living fiber, yet they present a constant form, may be demonstrated in fresh material, and are always present in osmic preparations They occur only in myelinated fibers with a neurilemma. These incisures subdivide the interannular segments of the myelin sheath into *myelin segments*. Schmidt originally considered them to be the optical expression of folds in the outer fibrous coats. Lantermann and others claim to have shown that they are within the neurilemma. They are believed by others to represent the limits of cones of neurokeratin The incisures may point in different directions. Bito[10] claims that they consist of protein material in contrast with the adjacent lipoid

[9] Tashiro, 1913.
[10] Bito, 1926

fiber, and upon the presence or absence of these sheaths nerve fibers may be classified as follows:

A. Myelinated nerve fibers.............. $\left\{\begin{array}{l}\text{1. With a neurilemma}\\\text{2. Without a neurilemma}\end{array}\right.$

B. Unmyelinated nerve $\left\{\begin{array}{l}\text{3. With a neurilemma}\\\text{4. Without a neurilemma—alemmal}\end{array}\right.$
fibers

Myelinated Nerve Fibers with a Neurilemma.—Nearly all the nerve fibers of the cerebrospinal nerve trunks and ganglia and some of those of the sympathetic nerves are of this type. These nerve fibers consist essentially of three cylindrical structures: the *axis cylinder,* which is the continuation of the axon of a nerve cell, and which forms the central portion or core of the nerve fiber; the *medullary (myelin) sheath,* which forms a hollow cylinder inclosing the axis cylinder, and which suffers frequent interruptions, as will be described; and the *neurilemma,* which is an extremely thin investing sheath forming an uninterrupted envelope from the point where the nerve fiber leaves the central nervous system to a point near the end of the fiber where the axis cylinder breaks into its terminal fibrils. To these structures an investing sheath of connective tissue, the *sheath of Henle,* is sometimes added. It is derived from the connective tissue *endoneurium* in which the nerve fibers are embedded. It serves to support the capillary blood-vessels destined for the supply of the nerve fibers.

The Axis Cylinder.—The axis cylinder presents a finely fibrillar structure. The nature of these fibrils is not well understood. They are apparently continuous with the neurofibrillar network of the cell body.

In certain nerve fibers of the lower animals these fibrils have a tendency to collect into the center of the axis cylinder, leaving a peripheral clear zone; this distribution is especially characteristic of those fibers which are not supplied with a myelin sheath In mammals, however, the fibrillae occupy a larger portion of the axis cylinder, the clear peripheral area being correspondingly diminished until in man it can scarcely be recognized. The fibrils of the lower animals are also coarser.

Apáthy, studying chiefly the lower animals, has considered these *ultimate fibrillae* to be the conducting element of the nerve fiber. Others, however, lay greater stress upon the intervening clear portion, the *neuroplasm* of Schieffer-decker or *axoplasm,* as containing the active conducting substance of the fiber This is also the view of Parker,[8] who concludes further that the neurofibrils are the parts of the neuron especially concerned with the metabolism of its more distant parts, and not with the conduction of nerve impulses. According to this interpretation nerve fibrils are trophic elements.

According to Verworn, Lenhossék and R. Goldschmidt, these elementary fibrillae (axon fibrils) in the axis cylinder are nothing else than skeletal substance for the support of the semifluid neuroplasm. The circumstance that many of the fibrils of an axis cylinder may be sectioned without diminution of the

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[8] Parker, 1929.

myelin, and he ascribes to them a nutritive function. They are more probably artifacts, representing fractures in the delicate myelin sheaths.

In preparation of fresh nerve fibers which have been treated with silver nitrate according to the method of Ranvier, the solution is found to enter the fiber most readily at the nodes of Ranvier, so that if blackened by exposure to the sunlight, minute +-like appearances are seen at each node. By prolonged maceration in weak solutions of silver nitrate the solution penetrates still farther and the blackened axis cylinder is found to possess spiral transverse markings which are quite characteristic. The true meaning of these appearances has not been satisfactorily explained. Because of the apparent greater permeability of the fiber at these points, these peculiarities have been taken to indicate a certain relation of the annular constrictions to the nutrition of the fiber.

The Neurilemma (Nucleated Sheath of Schwann).—The neurilemma is the outermost of the nerve fiber sheaths. It is of ectodermal origin and makes its appearance prior to the myelin sheath It forms a very delicate membrane, which incloses the myelin substance, and at each node of Ranvier comes into contact with the axis cylinder

Attached to the inner surface of the neurilemma in each internode, and usually but one for each internodal segment, is an oval nucleus. The nucleus is surrounded by a minute amount of finely granular cytoplasm. This structure is taken to indicate that the embryonal

FIG. 160.—CROSS-SECTION OF THE TRUNK OF THE HUMAN VAGUS NERVE, SOME DISTANCE BELOW THE NODOSE GANGLION, SHOWING MYELINATED AND UNMYELINATED FIBERS.

Pyridine silver. ×680 (Ranson.)

neurilemma is formed by cells (*lemmocytes*) which became spread out over the surface of the primitive fiber, one cell, as a rule, supplying each internodal segment; and its nucleus with a minute amount of undifferentiated protoplasm is, according to this hypothesis, considered to remain as a permanent part of the neurilemma.

Myelinated Nerve Fibers without a Neurilemma.—This type of nerve fiber composes the white matter of the central nervous system. The axis cylinder does not, of course, differ in the least from those of the previous variety and will need no further description

The myelin sheath also is similar in its finer structure to that of the previous type, but since no neurilemma is present, these fibers possess no nodes of Ranvier. The myelin sheath of the fibers found in the white matter of the brain and spinal cord is therefore uninterrupted Its surface is in direct contact with the neuroglia

FIG. 156.—MYELINATED FIBERS FROM THE NERVUS ISCHIADICUS OF THE FROG, TREATED WITH 1 PER CENT SOLUTION OF OSMIUM TETROXIDE.

A, lower magnification (×70), showing one complete internodal segment of a length of about 200 microns. *B*, higher magnification (×500), showing Schmidt-Lantermann incisures (*J*) *SR*, node of Ranvier, *K*, nucleus of neurilemma (*H*); *M*, myelin; *N*, axis cylinder. (Schaffer.)
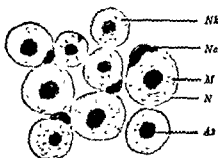
FIG. 158.—A GROUP OF LARGE MYELINATED FIBERS FROM A NERVE IN THE PERITRACHEAL AREOLAR TISSUE OF THE CAT.

Ax, axis cylinder; *Nk*, neurokeratin framework; *Nr*, neurilemma cell and nucleus; *M*, myelin sheath; *N*, neurilemma, ×1000.

FIG. 159.—CROSS AND LONGITUDINAL SECTIONS OF THE SAME FUNICULUS.

(*N*) unmyelinated nerve fibers (turned up at the left), showing the perineurium (*P*) and the relation of the neurilemma nuclei to the axis cylinder bundles of neurofibrils. From the peritracheal areolar tissue of the cat. ×1500.

of origin for its nutrition. Each nucleus therefore becomes the trophic center for the fiber tract to which it gives origin.

It may be readily demonstrated that if any such group of axons be cut or otherwise separated from its trophic center, that tract will promptly degenerate. If these axons happen to be the axis cylinders of medullated nerve fibers, as is often the case, their myelin sheaths become rapidly altered in composition and acquire a tendency to disintegrate into small globular granules, which stain deeply with osmic acid when used according to the method of Marchi. For the experimental demonstration of this form of partial cell death occurring in that portion of the neuron which has been cut off from its cell of origin, we were originally indebted to the eminent English physiologist Waller; the resulting changes are therefore called *wallerian degeneration*.
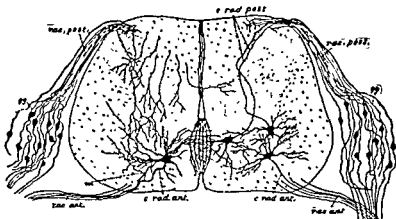
FIG 161—TRANSECTION OF THE SPINAL CORD OF AN EMBRYO CHICK.

c. rad ant, axons to the ventral roots; *c. rad. post*, axons to the dorsal roots; *col*, collateral from an axon back to the gray matter; *gg*, dorsal root ganglion; *rac. ant.*, ventral root; *rac. post.*, dorsal root. (van Gehuchten)

Obviously that portion of a neuron or of a fiber tract which, after injury or disease involving its path, still retains its connection with its cell body or trophic center, will not degenerate. This part of the neuron is called its *central portion*, in contradistinction to its *distal portion*, the latter of which has been severed from its trophic center and is consequently degenerated. The degeneration following section of a myelinated nerve involves also the central end to the point of the first node of Ranvier, occasionally to a point several nodes beyond the first.

The histologic difference between dendrons and axon imposes on the neuron a sharp structural and functional polarity. The latter is correlated with the fact, expressed in Sherrington's law of forward direction, that the nervous impulse passes across the area of contiguity between dendron and axon (the synapse) in vertebrates only in one direction, that is from axon to dendron.

The entire central nervous system contains a fundamental meshwork of delicate unmyelinated fibrils, the so-called *neuropil*. In certain localized portions of the spinal cord and brain the neuropil is relatively denser and enters into the composition of the so-called reticular formations.

network, which forms the supporting tissue of these organs, the innermost layer being condensed into a membrane which simulates a neurilemma. These fibers are accompanied by *sheath cells*, homologues of the neurilemma cells of other fibers, which aid in the formation and maintenance of the myelin.

Unmyelinated Nerve Fibers with a Neurilemma (*Sympathetic Nerve Fibers, Remak's Fibers*).—Most of the fibers of the sympathetic division are of this type. The axis cylinder does not differ from that of the previous types. The myelin sheath is entirely absent or, at most, only slightly developed in these fibers. The neurilemma is perhaps universal at times, but exhibits frequent nuclei along the course of the fiber. The neurilemma nuclei appear to be embedded in the superficial portion of the axis cylinder. *Fibers of this type are of quite frequent occurrence* also in the cerebral (cephalic; cranial) nerves of the cerebrospinal division. Other cerebrospinal nerve fibers lose their myelin sheath and finally also their neurilemma prior to their termination.

The work of Ranson [11] has shown that even in the typical myelinated spinal and cerebral nerves *unmyelinated fibers are very abundant. In the vagus of the dog,* for example, the unmyelinated fibers actually preponderate below the diaphragm. Ranson states that of these no considerable portion can be of sympathetic origin and that only a few represent medullated fibers which have lost their myelin distally.

The unmyelinated fibers of the vagus are said to comprise both afferent and efferent fibers, the former arising from cells in the ganglia (jugular and nodose) connected with the vagus nerve. The spinal nerves also are shown to contain more unmyelinated than myelinated fibers. [12]

Unmyelinated Nerve Fibers without a Neurilemma.—These fibers are naked axis cylinders and as such are found at the cytoproximal end of the axon in the gray matter of the central nervous system, and at the cytodistal end prior to the termination of the axon in its arborization of terminal fibrils. In man nerve fibers are of this type throughout their entire course only in the olfactory nerves.

All portions of the neuron, its axon and collaterals as well as its dendrons, are dependent upon the cell body for nutrition; hence each nerve cell becomes the so-called *trophic center* for all of its processes.

The entire nervous system may be considered as an enormous tangle, formed by the interlacing processes of an innumerable number of neurons whose complex fiber paths place all portions of the body in communication with all other portions.

Nerve cells are unequally distributed throughout the central division of the nervous system; they therefore occur in more or less distinct groups or *nuclei*, from each cell of which an axon is frequently distributed along the same path. The larger bundles thus formed are called *funiculi, fasciculi,* or *fiber bundles;* the smaller ones, *tracts.*

Since each fiber of such a tract is dependent for nutrition upon the nerve cell from which it arises, the tract *as a whole must depend upon its nucleus*

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[11] Ranson, 1914.
[12] Ranson, 1911.

small cells with large and deeply staining nuclei. In the small glia cells the cytoplasm is so slight as to form scarcely more than a mere rim about the nucleus; in the larger cells the cytoplasm is more abundant and the processes larger and more numerous. The presence of cytoplasmic processes gives the cell an irregularly stellate appearance. In Golgi's preparations these processes cannot be distinguished from the dense network of gray glia fibers with which they are surrounded.

FIG. 163.—PORTION OF GRAY SUBSTANCE FROM THE ANTERIOR HORN OF THE SPINAL CORD OF MAN, SHOWING NERVE CELL BODIES, DENDRONS, MYELINATED AND UNMYELINATED POR- TIONS OF AXONS, AND NEUROGLIA.

(Weigert-Pal stain.)

The Glia Fibers.—The glia fibers comprise numerous filiform fibrils which occur as a dense network around the glia cells, from which they radiate in all directions. They pass alongside of, over, or under the glia cells; their filaments have even been described as passing entirely through the cytoplasm of the cell. Nevertheless they appear at all points to be anatomically distinct from the cell body.

The relation of the glia cells to the fibers of neuroglia is perhaps comparable to the arrangement in fibrous or reticular tissue. The fibers of each of these tissues appear to be ontogenetically derived either directly or indirectly from its cells, yet when fully formed they often exist as anatomically distinct elements.

Occurrence of Neuroglia.—Neuroglia cells and fibers occur in both gray and white matter of the central nervous system, though perhaps more abundant in

NEUROGLIA

Both the gray and the white matter of the central nervous system contain a peculiar supporting or *interstitial* tissue, the *neuroglia*, which consists of two elements, the *glia cells* and *glia fibers*. The latter are very probably produced by the glia cells, of which they were formerly considered to be processes. They consist of a substance similar to, perhaps identical with, the neurokeratin framework of myelin.
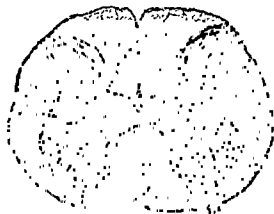
FIG. 162.—TRANSECTION OF THE SPINAL CORD OF A CHILD, FIFTH LUMBAR SEGMENT.

The central H-shaped gray substance consists of nerve cell bodies, dendrons, unmyelinated portions of axons, and neurogliar supporting tissue The enveloping white substance consists of myelinated axons supported by neuroglia. Weigert stain. ×7.

The **Glia Cells.**—The glia cells, as seen in Golgi preparations, are divisible into two distinct types, the *ependyma cells* and the *astrocytes (gliocytes)*.

The *ependyma cells* may be considered as undifferentiated relics of the embryonal cells, from which both glia and true nerve or ganglion cells were developed. These cells line the central canal of the spinal cord and the ventricles of the brain, in which latter organ they also form the covering or outer coat of the telae choroideae.

The ependyma consists of long nucleated columnar cells whose free ends, in fetal and early life, carry a tuft of cilia; in adult life they are usually nonciliated. The attached ends of these cells are embedded in the surrounding gelatinous tissue, and are frequently prolonged for some distance as a fine branched process. In this way the ependyma of the spinal cord enters into the formation of the central gelatinous substance, in which the branched processes of its cells ramify in a glia-like manner. In the fetus the filamentous processes extend from the central canal all the way to the periphery of the spinal cord. In the adult the ependyma cells are prone to multiply so as almost to occlude the central canal; their processes have apparently become shorter, and now reach the surface of the spinal cord only at its dorsal median sulcus.

The *astrocytes*, when stained by the Golgi method, apparently consist of a small cell body and an innumerable number of long slender processes. Two varieties of these cells are recognized: the *spider cell* or *long-rayed astrocyte*, with a small cell body and very many exceptionally long and slender processes; and the *mossy cells* or *short-rayed astrocytes*, whose processes are shorter and somewhat thicker but decidedly more varicose than those of the long-rayed type.

Investigations by means of the staining methods of Weigert, Mallory, and Benda, have demonstrated that the astrocytes, as seen in the Golgi preparations, probably include two distinct structures, the glia cells and the glia fibers.

Glia cells, as seen in sections prepared according to these methods, appear as

the latter. The fibers radiate for considerable distances from their glia cells, and thus form a supporting tissue for the nerve elements. They are frequently in intimate relation with the blood vessels, on the walls of which many of the
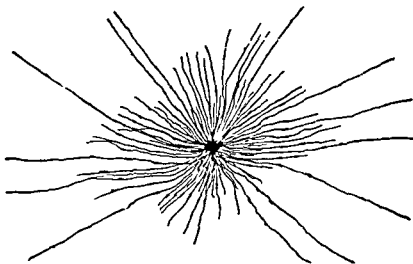
Fig 166 — A Long-rayed Astrocyte.
Golgi's stain Highly magnified (Berkley)

glia fibers, particularly the thicker or mossy variety, terminate in expanded plates, which, in some parts, form an almost complete outer membranous coat of the vessel.

The astrocytes are ontogenetic derivatives of the embryonic ependyma cells. From their point of origin around the neural canal they wander to all portions of the central nervous system, and even into the optic and olfactory tracts, which are embryonic outgrowths from the fetal cerebral vesicles Thus neuroglia occurs throughout the brain and spinal cord, and also in the olfactory nerves, the optic chiasm, and the retina of the adult.

The supporting tissues of the central nervous system include, besides the neuroglia, numerous bands of trabeculae of fibrous connective tissue, which push inward from the pia mater, carrying with them the vascular branches for the supply of the nervous tissues, and which penetrate deeply into the substances of the spinal cord and brain.

Fig. 167. — A Short-rayed Astrocyte, or Mossy Cell.
Golgi's stain. Highly magnified. (Berkley.)

On the basis of an improved staining technic for neuroglia, Del Rio-Hortega (1919) proposed a new terminology. This terminology is now in general use. It applies in part to newly revealed elements of the neuroglia, in part to the well-recognized astrocytes. The matter may be summarized as follows:

I. Astroglia (Macroglia) { 1. Protoplasmic astrocytes
2 Fibrous astrocytes
II. Oligodendroglia (olioglia)
III. Microglia (mesoglia)

FIG 164.—TRANSVERSE SECTION THROUGH THE WHITE SUBSTANCE OF THE HUMAN
SPINAL CORD

The dark oval bodies are cross-cut axis cylinders; the surrounding light halos represent the myelin sheath. The coarser trabeculae are connective tissue, continuous with the finer neuroglia framework. (Weigert-Pal stain.)
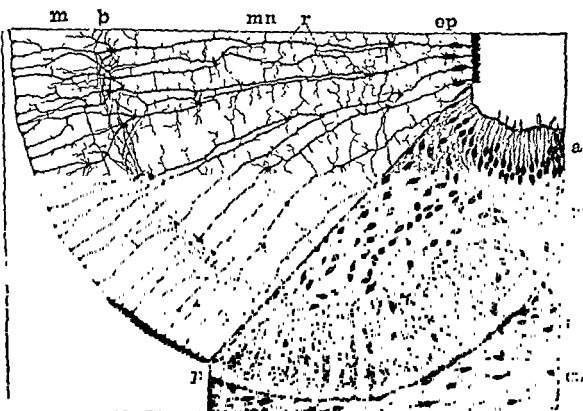
FIG. 165.—NEUROGLIA FROM THE SPINAL CORD OF A FETAL PIG.

The portion above shows the result of the Golgi stain; below, that of a hematein and Congo red stain. *a*, inner layer of neuroglia, adjoining the central canal; *b*, boundary between the ⋯⋯⋯⋯ tissue; *ep*, ependyma; *m*, mantle layer; ⋯⋯⋯ raphe; *p*, pia mater; *r*, radial filaments
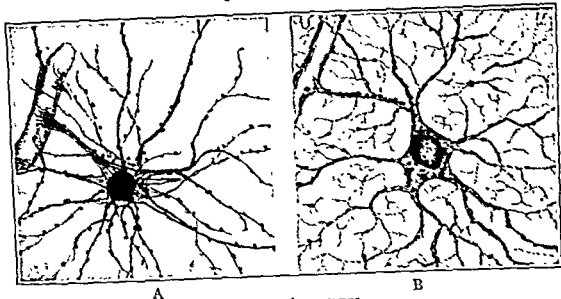
FIG. 170.—ASTROCYTES.

A, fibrous variety. The processes show varicosities, the gliosomes. Several processes are shown ending in expansions (perivascular feet) on a blood vessel. *B*, protoplasmic variety, with gliosomes and perivascular feet. (Penfield and Cone.)

prises small neuroglia cells with only a few short processes (Fig. 171). They lack fibers and perivascular feet; their processes are more delicate and branch less extensively than is the case with astroglia. In other cytologic features, gliosomes, Golgi apparatus, and centrosome, they are like the astrocytes. Olioglia is divisible into *interfascicular glia* (sheath cells) occurring in the white matter, where rows of cells form incomplete sheaths for the myelin; *perineuronal satellites*, forming incomplete sheaths for the neurocytes of the gray matter and *perivascular satellites*, cells
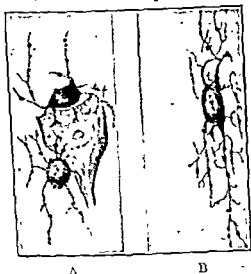
FIG 171.

FIG 172.

FIG. 171.—OLIGODENDROGLIA.

A, satellite cells This variety, of stellate form, occurs as perineuronal glia in the gray matter. *B*, interfascicular oligodendroglia. This variety occurs in the white matter of the brain and cord. (Penfield and Cone.)
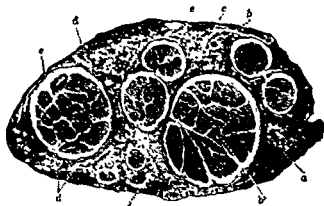
FIG. 172.—TRANSECTION OF THE SCIATIC NERVE OF A DOG.

The fat cells and the myelin sheaths of the nerve fibers have been blackened by osmium tetroxide. *a*, fat cells, *b*, *b'*, blood vessels, that at *b'* lies within a funiculus; *c*, epineurium; *d*, perineurium; *e*, coarser bands of the endoneurium. Osmium tetroxide. Photo. ×30.

The microglia (Fig. 169) are perhaps not strictly glia cells. They are thought to originate from mesoderm introduced with the pia mater covering invading blood vessels, and to function as macrophages. However, the experiments of Harvey and Burr [18] show that at least in the salamander the pia mater arises from neural crest cells, hence ectodermal in origin like astroglia and olioglia.

The *protoplasmic astrocytes* are large stellate elements with extensively branching nonfibrous processes (Fig. 170B). These cells correspond to the mossy neuroglia cells of the earlier terminology. The processes are characterized by numerous small spheroidal swellings caused by the presence of granules. These granules occur also in the main body of the cell and constitute the *gliosomes*. According to one interpretation they represent mitochondria; they are also interpreted as secretion granules. A Golgi apparatus may be demonstrated in young astrocytes, appearing as a small juxtanuclear net in the base of the largest process. A centrosome also is demonstrable. The protoplasmic astrocytes are practically restricted to the gray matter of the brain and spinal cord. One or several of the processes may attach themselves by a terminal expansion, the perivascular foot (podic), to blood vessels.

FIG. 168—NEUROGLIA CELL WITH ADJACENT FIBERS FROM THE PINEAL BODY OF A YEARLING SHEEP. ×1500

Fibrous astrocytes are the long-rayed "spider" cells of the older terminology. The processes are longer, straighter and less numerous than those of the protoplasmic astrocytes Certain processes may end in fibrous perivascular feet (Fig. 170A). The cytoplasm contains gliosomes, a centrosome, and, in young cells, a Golgi apparatus. The differential character of these cells concerns the presence of numerous glia fibers. The fibers occur both within the cytoplasm, where they originate, and secondarily to some extent extracellularly. Cajal recognized also a rare *mixed type* of astrocyte, with both protoplasmic and fibrous processes.

Oligodendroglia (olioglia of Hortega) com-

FIG. 169—MICROGLIA.

These cells are of mesodermal origin and constitute the macrophages of the brain and cord. (Penfield and Cone.) Two neurocytes and one microglia cell are shown.

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[18] Harvey and Burr, 1924

Nerve trunks frequently branch, the branches being formed either by an individual funiculus or by groups of funiculi. In the smaller nerve trunks the funiculi are further subdivided. It is by anastomosis of the funiculi that most of the nerve plexuses are formed. Individual nerve fibers of the myelinated type do not generally branch except in those portions which are naked axis cylinders, *viz.*, at the cytoproximal portion of the axon by means of collaterals, and at the cytodistal portion by means of end arborizations. Occasionally also collaterals arise at a node of Ranvier.

Vascular Supply.—The nerve trunks are well supplied with *blood vessels*. The larger of these are found in the epineurium, and from them branches of considerable size enter the septa to be distributed throughout the perineurium to the funiculi.

FIG. 174—AREA OF GASSERIAN GANGLION OF MAN ×1200

The coarser septa of the endoneurium contain minute arterioles and venules. A capillary network with elongated meshes occupies the finer divisions of the endoneurium, its vessels being thus brought into contact with the nerve fibers.

Perivascular *lymphatic vessels* abound in the epineurium and its septa, and lymphatic tissue spaces are found throughout the connective tissue of the nerve trunk. Where the cerebrospinal nerve trunks penetrate the meninges these lymphatic vessels are said to be continuous with the similar vessels of the dura mater.

Minute nerve fiber bundles, *nervi nervorum*, are also found in the epineurium; their fibers are mostly, if not entirely, distributed to the blood vessels.

attached to blood vessels both in the white and gray matter. Certain myelinated fibers of the cord, with fairly complete sheaths of olioglia, may show typical incisures of Schmidt. In terms of this classification the neurilemma of the peripheral nerves and the nucleated capsule of the cell bodies of the cerebrospinal ganglia consist of oligodendroglia.

Ependymal cells, under this classification, are regarded as *spongioblasts (glioblasts),* serving as ancestors of astrocytes.

NERVE TRUNKS

Structure.—The nerve fibers of the peripheral nervous system are united into bundles to form the *nerve trunks* or *nerves.* Each nerve is surrounded by a heavy connective tissue sheath, the *epineurium,* which sends trabecula-like septa into the nerve. These septa subdivide the nerve trunk into smaller bundles of nerve fibers, the funiculi. The *funiculus* forms a compact bundle of nerve fibers, and is in turn invested with a sheath of dense connective tissue, the *perineurium.* Hence the perineurium stands in the same relation to the funiculus as does the epineurium to the whole nerve trunk.

From the inner surface of the perineurium, septa pass into the funiculus and break up to form a fine connective tissue framework, the *endoneurium,* for the support of the individual nerve fibers. On separating the fibers of a funiculus with needles a portion of this fibrous

FIG. 173—DIAGRAM OF THE ORIGIN AND RELATIONS OF THE PERIPHERAL MOTOR AND SENSORY NEURONS.

A cylindrical section of the spinal cord, with its ventral and dorsal nerve roots, is shown *a,* the nerve cell of the ventral horn whose axon passes through the ventral nerve root, *b,* to its peripheral termination, *c;* at *d* is a unipolar sensory nerve cell in the dorsal root ganglion; its process immediately divides into a peripheral and a central branch. The central branch enters the spinal cord and at *e* divides into an ascending, *f,* and a descending, *g,* branch from both of which numerous collaterals, *h,* enter the gray matter and terminate in fine end-brushes. The peripheral branch of the spinal ganglion cell enters a spinal nerve and finds its way to its termination which is here represented in the skin; it terminates partly by free endings among the epithelial cells, *i,* and partly in connection with a sensory end-organ, *k,* in this case a tactile corpuscle of Meissner. (von Lenhossék.)

endoneurium remains adherent to the surface of the nerve fiber and gives the appearance of an outermost fibrous sheath, the so-called connective tissue *sheath of Henle.*

Nerve trunks frequently branch, the branches being formed either by an individual funiculus or by groups of funiculi. In the smaller nerve trunks the funiculi are further subdivided. It is by anastomosis of the funiculi that most of the nerve plexuses are formed. Individual nerve fibers of the myelinated type do not generally branch except in those portions which are naked axis cylinders, *viz.*, at the cytoproximal portion of the axon by means of collaterals, and at the cytodistal portion by means of end arborizations. Occasionally also collaterals arise at a node of Ranvier.

Vascular Supply.—The nerve trunks are well supplied with *blood vessels*. The larger of these are found in the epineurium, and from them branches of considerable size enter the septa to be distributed throughout the perineurium to the funiculi.

Fig. 174—Area of Gasserian Ganglion of Man. ×1200.

The coarser septa of the endoneurium contain minute arterioles and venules. A capillary network with elongated meshes occupies the finer divisions of the endoneurium, its vessels being thus brought into contact with the nerve fibers.

Perivascular *lymphatic vessels* abound in the epineurium and its septa, and lymphatic tissue spaces are found throughout the connective tissue of the nerve trunk. Where the cerebrospinal nerve trunks penetrate the meninges these lymphatic vessels are said to be continuous with the similar vessels of the dura mater.

Minute nerve fiber bundles, *nervi nervorum*, are also found in the epineurium; their fibers are mostly, if not entirely, distributed to the blood vessels.

attached to blood vessels both in the white and gray matter. Certain myelinated fibers of the cord, with fairly complete sheaths of olioglia, may show typical incisures of Schmidt. In terms of this classification the neurilemma of the peripheral nerves and the nucleated capsule of the cell bodies of the cerebrospinal ganglia consist of oligodendroglia.

Ependymal cells, under this classification, are regarded as *spongioblasts* (*glioblasts*), serving as ancestors of astrocytes.

NERVE TRUNKS

Structure.—The nerve fibers of the peripheral nervous system are united *into bundles to form the nerve trunks* or *nerves*. Each nerve is surrounded by a heavy connective tissue sheath, the *epineurium*, which sends trabecula-like septa into the nerve. These septa subdivide the nerve trunk *into smaller bundles of* nerve fibers, the funiculi. The *funiculus* forms a compact bundle of nerve fibers, and is in turn invested with a sheath of dense connective tissue, the *perineurium*. Hence the perineurium stands in the same relation to the funiculus as does the epineurium to the whole nerve trunk.

FIG 173—DIAGRAM OF THE ORIGIN AND RELATIONS OF THE PERIPHERAL MOTOR AND SENSORY NEURONS.

A cylindrical section of the spinal cord, with its ventral and dorsal nerve roots, is shown. *a*, nerve cell of the ventral horn whose axon passes through the ventral nerve root, *b*, to its peripheral termination, *c*; at *d* is a unipolar sensory nerve cell in the .... immediately divides

both of which numerous collaterals, *h*, enter the gray matter and terminate in fine end-brushes. The peripheral branch of the spinal ganglion cell enters a *spinal nerve* and finds its way to its termination which is here represented in the skin; it terminates partly by free endings among the epithelial cells, *i*, and partly in connection with a sensory end-organ, *k*, in this case a tactile corpuscle of Meissner. (von Lenhossék.)

From the inner surface of the perineurium, septa pass into the funiculus and break up to form a fine connective tissue framework, the *endoneurium*, for the support of the individual nerve fibers. On separating the fibers of a funiculus with needles a portion of this fibrous

endoneurium remains adherent to the surface of the nerve fiber and gives the appearance of an outermost fibrous sheath, the so-called connective tissue *sheath of Henle*.

In the ganglia of the acoustic nerve the primitive bipolar condition of the neuron is retained; and the cell body is not surrounded by a capsule.

The nerve cells of all other ganglia are surrounded by a capsule of flat epithelioid cells which form a complete investment for the nerve cell and its processes, being continuous with the neurilemma. The capsule is not, however, as a rule, closely applied to the cell, but leaves a narrow interval which is occupied by lymph or "tissue juice." The capsule and the neurilemma represent neuroglia (oligodendroglia).

In their structure the ganglionic neurons do not appear to differ in any way from other neurons. The large vesicular nucleus with its distinct nucleolus readily distinguishes these cells from those of neighboring tissues.

The studies of the ganglion cells by Dogiel, Ranvier, and Cajal have done much to explain the relations of these cells to each other, especially in the sympathetic system, where they were formerly but little understood. In the *spinal ganglia* Dogiel [14] describes two types of ganglion cells: (1) a unipolar cell in which the axon is thick and frequently proximally convoluted and, after branching in T-shape fashion, passes out of the ganglion to become the axis cylinder of a myelinated nerve fiber, and (2) cells with a slender axon which breaks up within the ganglion and whose terminal arborizations form a pericapsular plexus around the cell capsule; from this plexus fine end branches penetrate the capsule to form a pericellular arborization about the nerve cell itself. The cells of this latter type suggest association neurons within

FIG. 177.—SCHEMATIC REPRESENTATION OF THE RELATIONS OF THE STRUCTURES COMPOSING A SPINAL GANGLION.

A and *B*, ventral and dorsal spinal nerve roots; *C*, a spinal nerve; *D* and *E*, its ventral and dorsal divisions; *F*, its ramus communicans. *a*, nerve cells of the first type, whose axons divide and form the axis cylinder of a peripheral and a central nerve fiber; *b*, nerve cells of the second type, whose axons, *n*, end in a felt-work about the cells of the first type; *s*, sympathetic nerve fibers which terminate in a basket-work about the cell bodies of the second type of ganglion cells (Dogiel).

the ganglion. Nerve fibers from the sympathetic ganglia also enter the spinal ganglia and form pericellular arborizations about the cells of the second type. Dogiel found also that multipolar ganglion cells occur in the spinal ganglia of the adult as well as of the embryo.

[14] Dogiel, 1896.

GANGLIA

A ganglion may be described as a group of nerve cells occurring in the course of a peripheral nerve trunk. The largest of the ganglia form fusiform swellings in the course of the nerve, which are visible to the naked eye. The smallest, on the other hand, contain not more than half a dozen nerve cells, and these must be sought with the aid of the microscope and can only be found by the most careful observation.

Whatever may be their size, all ganglia appear to have a similar structure, except for those differences which characterize the sympathetic as distinguished from the cerebrospinal type. The essential elements of structure are the nerve cells, nerve fibers, and a supporting framework of rather dense fibro-elastic connective tissue.
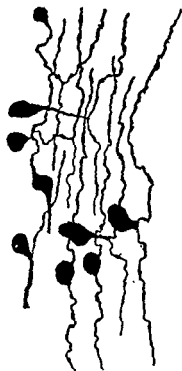
FIG. 175
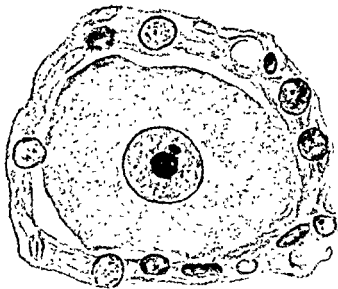
FIG. 176.

FIG. 175.—TRANSFORMATION OF BIPOLAR CELLS INTO UNIPOLAR CELLS IN THE GASSERIAN GANGLION OF THE PIG.

(Barker, after van Gehuchten.)

FIG 176—GANGLION CELL AND NUCLEATED CAPSULE FROM GASSERIAN GANGLION OF MAN ×800.

Many of the nerve cells of the adult mammal are unipolar in the cerebrospinal ganglia, but are usually multipolar in the sympathetic. The spinal ganglia of the lower vertebrates and of the embryo mammal, however, contain bipolar ganglion cells. In mammals the two processes of the embryonal neuron fuse to form a single one which branches in a Y- or T-like manner soon after leaving the parent cell body.

or less extensively forming the fenestrated variety of cells. The axon, prior to its division, may split at one or several points, for longer or shorter distances, into two or many portions, and reunite again into a single fiber; rarely also the axon may have two or more points of origin, probably the result of fusions of collaterals with the cell body. These more complex atypical forms are said to predominate in man. Ranson [16] regards them to some extent at least as transient modifications, which may return to the simpler unipolar condition. Nageotte [17] has suggested that the phenomena of end-disks and fenestrations signify regenerative activity. They are relatively more abundant in regenerating transplanted ganglia. But they are abundant also in pathological ganglia, and in fetal ganglia.[18] No conclusive evidence has yet been presented that these modified forms signify functional derangement. A variable small number of the neurons of the ganglia, especially in the sympathetic ganglia adjoining the urinary bladder, are multinucleated.[19]

SYMPATHETIC DIVISION OF THE NERVOUS SYSTEM

The sympathetic division of the nervous system consists anatomically of three sets of ganglia: (1) the ganglionated cords (sympathetic trunks; vertebral ganglia); (2) the prevertebral plexuses; and (3) the visceral or terminal plexuses, including chiefly the myenteric and submucous plexuses of the alimentary canal. The ganglia of the ganglionated cords are segmentally arranged, and interconnected transversely (caudally) and longitudinally by plexuses of unmyelinated fibers. They are connected also with the spinal nerves by the *white* and *gray rami communicantes*. Homologous ganglia in the head region, less definitely related to the cerebral nerves, are the ciliary, sphenopalatine, submaxillary, sublingual, parotid and otic ganglia. The prevertebral plexuses develop from nonsegmentally arranged primordia which originate as outgrowths at certain levels of the early ganglionated cord. These plexuses contain fewer and smaller cells, with a preponderance of fibers, *e.g.*, cardiac, celiac (semilunar; solar), hypogastric and pelvic plexuses. The myenteric and submucous plexuses are located in the muscle and submucous layers respectively of the esophagus, stomach and intestines. Here the cells are still smaller and less numerous than in the prevertebral plexuses, and the fiber-network is less dense. A plexus is a network of nerve fibers with few cells; where the nerve cells are relatively abundant, the plexus is known as a ganglion. The embryonal cells (neuroblasts) which develop into sympathetic neurons have migrated from the neural crest, and in part from the ventral wall, of the primitive spinal cord.[20] Jones interprets the experimental evidence from chick embryos as favoring the view "that the source of most, if not all, of the neuroblasts that form the sympathetic trunks, is the neural tube." [21]

[16] Ranson, 1914
[17] Nageotte, 1907.
[18] Huber, 1913
[19] Beaton, Holmes and Windle, 1939
[20] Raven, 1937.
[21] Jones, 1937.

The later studies of Cajal (1905), Dogiel (1908), and Ranson (1912) have revealed a third distinct type of cell formerly apparently included under Dogiel's Type I: smaller, pyriform, unipolar cells with unmyelinated axon, rarely convoluted dividing into a central and a peripheral branch, the exact terminations of which are unknown; but having according to Ranson [15] apparently the same distribution as the coarser myelinated fibers of Type I, and probably afferent in nature. In cat and rat Ranson estimates the number of these cells at two-thirds that of the total number. These are the cells which contribute the bulk of the very numerous

FIG 178.—COMMON ATYPICAL, THOUGH PROBABLY NORMAL, NERVE CELLS FROM THE SPINAL GANGLION OF THE DOG.

a and *b*, cells with collaterals ending in end-bulbs, *c*, a multipolar cell; *d* and *e*, fenestrated cells. (Ranson.)

unmyelinated fibers of the spinal nerves, only a small portion of which are believed to arise in sympathetic ganglia.

With the exception of relatively few cells of bi- and multipolar form, all of the nerve cells of the spinal ganglia are unipolar in the adult condition. In the case of the larger cells, the myelinated axon before leaving the capsule is more or less extensively convoluted over the cell body forming in the extreme condition a so-called "glomerulus." These same cells are variously modified by the presence of short, coarse and fine intra- and extracapsular processes (both dendrons and collaterals) frequently terminating in "end-disks." Such processes may fuse more

15 Ranson, 1911.

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In the *sympathetic* (or autonomic) ganglia Dogiel [23] likewise recognized two cell types, in general smaller than those of the spinal ganglia: (1) small multipolar fusiform or stellate nerve cells with 5 to 20 dendrons and an axon which enters the nerve trunks as an unmyelinated fiber, but may later acquire a thin myelin sheath—motor neurons; (2) larger spheroidal nerve cells with 1 to 16 dendrons and a single axon which also enters the nerve trunk as an unmyelinated nerve fiber, but may later acquire a very thin medullary sheath, perhaps sensory neurons. The dendrons of the second type are distinguished from those of the first by being very long and slender and also by entering the nerve trunks, to pass, presumably, to neighboring ganglia. The dendrons of the first cell type on the other hand, are shorter, thicker, and end in relation with other cells within the same ganglion. Carpenter and Conel report also intermediate types in the cat.

In certain rodents (rabbit and guinea-pig) many of the neurons of the vertebral and prevertebral autonomic ganglia are binucleate.[24]

The ganglionic cell group is excentrically placed as regards the axis of the nerve trunk, some funiculi apparently passing the ganglion without being in any way connected with its nerve cells.

FIG. 180.—THE SPROUTING OF AN AXON BY A NEUROBLAST FROM THE SPINAL CORD OF A FROG EMBRYO.

From a live specimen grown in lymph; the cell body is filled with yolk granules; the protoplasmic process (axon) is of hyaline appearance and undergoes ameboid movements. (Harrison.)

The sympathetic differ from the cerebrospinal ganglia chiefly in the relative preponderance of unmyelinated nerve fibers in the former and of the myelinated type in the latter. Just as the cerebrospinal ganglia receive a few unmyelinated sympathetic fibers, so also the sympathetic ganglia receive, through the medium of the white *rami communicantes*, a certain number of medullated nerve fibers from the cerebrospinal system. Moreover, with the intense staining method of Weigert, very thin myelin sheaths may now be demonstrated where formerly they were not suspected.

The sensory and motor neurons of the cerebrospinal division show characteristic differences in their chromophilic substance. In the cerebral and spinal ganglia the cell bodies of the sensory neurons contain fine Nissl granules evenly distributed throughout the cytoplasm. The motor cell bodies from the spinal cord contain fewer and much larger chromophilic flakes. The sympathetic neurons likewise present a characteristic and constant appearance: the chromophilic granules are intermediate in size and generally massed toward the periphery.

The ganglia are supplied with blood vessels and lymphatic vessels in a manner similar to the nerve trunks in whose course they occur.

The earlier conception of the nervous system interpreted the nerve fiber (axon)

[23] Dogiel, 1896.
[24] Carpenter and Conel, 1914.

Langley [22] employs the term "autonomic nervous system" (involuntary or vegetative nervous system) for all that portion of the peripheral nervous system not included among the cerebrospinal nerves, commonly designated as the "sympathetic system." This comprises four components: (1) the *sympathetic proper*, including the autonomic fibers arising from the thoracicolumbar regions of the spinal cord, together with the associated vertebral ganglia and their postganglionic neurons; (2) *sacral autonomic*, preganglionic fibers included in the roots of the second, third and fourth sacral nerves, together with the associated postganglionic neurons; (3)

FIG 179.—SYMPATHETIC NEURONS

A, in myenteric plexus, ileum of cat; *B* and *C*, in myenteric plexus, ileum of dog; *D, E, F*, in submucous plexus, ileum of dog; *a*, axon. *A* corresponds to Dogiel's Type I, a motor neuron; *B* and *C* correspond to Dogiel's Type II, probably sensory neurons. (Kuntz.)

cranial autonomic, a group of fibers arising from the midbrain and the medulla (this component is separated from the sympathetic proper by the whole extent of the cervical region of the spinal cord, which region lacks white rami communicantes); (4) *enteric*, including the myenteric and submucous plexuses of the digestive tube. Langley proposes also the term "parasympathetic" to designate the sacral and cranial autonomic fibers, since in many parts of the body they overlap the distribution of the sympathetic proper.

22 Langley, 1921.

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The earlier conception of the nervous system interpreted the nerve fiber (axon)

[23] Dogiel, 1896.
[24] Carpenter and Conel, 1914

as the fusion product of a chain of cells extending from its proximal to its distal end. The axis cylinder fibrils were regarded as differentiation products of the cytoplasm (Schwann; Apáthy; *et al.*). The view which now prevails interprets the axon as the outgrowth of the cell body to which it is attached (His; Cajal; *et al.*). The tissue culture work of Harrison[25] and others has established the outgrowth view upon a firm basis of observational data. By growing small pieces of the embryonic spinal cord of frogs in lymph, Harrison could observe the cells sprouting an axon process (Figs. 180, 181). He describes the beginning of a nerve fiber as an outflow of hyaline protoplasm from cells which were situated within the central nervous system. The experiments of Harrison upon frog larvae demon-

FIG 181—THE SPROUTING OF AN AXON BY A NEUROBLAST FROM THE SPINAL CORD OF A FROG EMBRYO

Two views of the same nerve fiber, grown in lymph, taken twenty-five minutes apart. (Harrison.)

strate further that the sheath cells of the neurilemma of motor and sensory fibers have their origin in the ganglionic crest, being therefore ectodermal, and that they are unessential to the formation of the fibrils of the axis cylinder. He excised the dorsal half of the cord, including the neural crest, and observed that in such larvae the fibers of the motor roots did not acquire sheath cells. On the contrary, when he excised the ventral half of the cord, dorsal root fibers developed normally with a neurilemma, but the sheath cells which migrated to the location where the ventral fibers normally appear were unable to produce these fibers in the absence of neuroblasts in the ventral half of the cord. Raven,[26] on the basis of xenoplastic transplantation experiments with urodele larvae (Triton taeniatus × axolotl), claims that the sheath cells are derived exclusively from the ventral part of the neural tube.

The influence which guides the nerve along its proper path is apparently exerted by the tissue which is to be innervated. The essential factors comprising this influence are obscure; they may be of a chemotropic nature. It must be emphasized, however, that the connection between a particular nerve and its tissue terminal is made relatively early, that is, while the two elements are still spatially relatively closely associated. Probably mechanical stimuli, inducing thigmotropic reactions, also play an important rôle in determining the path of a nerve fiber. The earlier relations are of course modified during growth; the definitive relation between nerve and end-organ is acquired by mutual adjustment. Harrison[27] has

[25] Harrison, 1908.
[26] Raven, 1937.
[27] Harrison, 1914.

contributed further experimental evidence in support of the view that the growing axon is guided through a stereotropic response.

By cultivating sympathetic neurons from pieces of the intestine of the embryo chick in saline solutions, W. H. and Margaret R. Lewis [28] have been able to demonstrate that here also the fibers arise as outgrowths of nerve cells.

NEURON THEORY

The work of Harrison, the Lewises, Speidel [29] and many others, including both experimental and morphological investigations, leave no further doubt of the accuracy of the *Neurone Theory* of Waldeyer (1891), which applies the cell theory of Schleiden and Schwann (1838–39) to the nervous system. It holds that the unit of structure is the neuron (neurocyte), consisting of cell body (cyton) and processes, including one axon, and one or several dendrons. The nervous system consists, accordingly, of innumerable associated neurons. Neurons arise each from a single embryonic cell, the neuroblast, retain their independence throughout life, and make connection with each other in general only by contact, which, however, is sufficiently intimate to insure functional continuity. A neuron exhibits a structural and functional polarity; and constitutes a trophic unit for the maintenance of whose metabolic activity a nucleus is necessary.

Further confirmation of the outgrowth interpretation as opposed to that of autogenesis of the axon has been furnished by the experiments of Clark [30] on the domestic fowl. By prolonged exclusive feeding of polished rice he induced degeneration in the peripheral myelinated nerves. On return to an adequately nutritive diet regeneration, accompanied by a return to normal locomotion and function, followed. The material thus gave opportunity for a microscopic study of the steps in the nerve degeneration and regeneration. When the degenerative process had not been excessively prolonged a new axis cylinder grew down the old myelin sheath, which returned to normal; when greatly prolonged the myelin disappeared and the nuclei of the neurilemma multiplied, giving an appearance *very similar to that* of embryonic nerve fibers (bandfasern stage). Clark concludes that the function of these excessive sheath cells is the removal of the degenerating myelin. The new myelin sheath is the product of joint influence of the new axis cylinder and the neurilemma cells, as demonstrated by the recent work of Speidel on living frog tadpoles. [31]

Mitochondria of granular and rod forms are abundant *in neuroblasts*. Meves, Duesberg and others have claimed that these differentiate into neurofibrils. The work of Cowdry [32] on chick embryos proves the untenability of this view. Cowdry showed that the neurofibrils arise as a differentiation of the ground substance of the neuroblast; and that mitochondria persist in undiminished numbers throughout the period of neurofibril

[28] Lewis, W. H. and Lewis, M. R., 1912.
[29] Speidel, 1932.
[30] Clark, 1914.
[31] Speidel, 1932.
[32] Cowdry, 1914.

development. Moreover, it is now known that mitochondria are present also in adult neurons They are apparently fundamental cytoplasmic constituents of a metabolically active cell.

Spinal ganglion cells of certain adult mammals (cat and rabbit) have been kept alive in tissue cultures for as long as twenty days.[33] The cells remain apparently normal, augment their amount of chromophilic substance, produce new neurofibrils, develop short processes with end-plates (neuropodia) and become fenestrated, but do not proliferate.

Speidel[34] has watched directly the entire process of nerve growth and ensheathment in the transparent tail fin of living frog tadpoles. The earliest nerve fibers grow outward as naked sprouts, each provided with an ameboid *growth cone* at the tip. Later the neurilemma sheath cells move along these, multiply by mitosis, and take up their stations at intervals. They form the tubular neurilemma. They aid in the formation of the myelin sheath. The myelin sheath is laid down in segments through the coöperative activity of the sheath cell and the axon. Each segment corresponds genetically to the zone of influence of one sheath cell.

In the brain and spinal cord occur in variable numbers peculiar irregular cells, resembling small neurogliar astrocytes in the usual preparations. These cells, the so-called *microglia*, or Hortega cells,[35] differ from the neuroglia cells in that they originate from mesoderm (pia mater; adventitia of blood vessels) and function as macrophages. They constitute the monocytes of the central nervous system, and assume great importance in certain pathological conditions. They are known also as *mesoglia*.

CHAPTER VI

PERIPHERAL NERVE TERMINATIONS: END-ORGANS

All peripheral nerve fibers end either as terminal fibrils or in relation to a highly specialized end-organ. The function of these latter bodies is apparently included in the changing of ordinary stimuli—mechanical, thermal, chemical, etc.—into a nerve impulse, or, *vice versa,* the changing of a nerve impulse to a cell stimulus which results in motion, secretion, etc., according to the nature of the tissue cells which are thus stimulated. Some of the nerve end-organs are connected with efferent (motor) fibers, others with afferent (sensory) fibers. Nerve endings are found in nearly all the tissues of the body with the exception of cartilage and the calcareous tissue of the bones.

NERVE ENDINGS IN EPITHELIUM

Intra-epithelial nerve fibrils are derived from the nerve fiber plexuses in the subjacent connective tissue; the epithelium usually receives a very abundant nerve supply. The following types of intra-epithelial nerve endings have to be considered.

End-fibrils.—This form of nerve termination has been demonstrated in all the varieties of epithelium. Terminal nerve fibers enter the epithelial tissue as naked fibrils, often somewhat varicose, which form a delicate plexus between the epithelial cells. The terminal fibrils of this plexus frequently end in minute knob-like enlargements which are in contact with the surface, but rarely, if ever, penetrate the interior of the epithelial cells. The "trefoil plates" of Bethe represent unusually large end knobs.
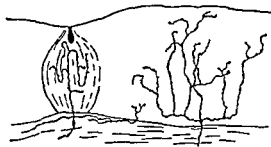
Fig. 182—Nerve Endings in the Epithelium of the Larynx.

On the left a taste bud; on the right, nerve endings in the stratified squamous epithelium are represented (Retzius)

Tactile Cells (of Merkel).—These are modified epithelial cells, with clear cytoplasm and a slightly vesicular nucleus, which are found in the deeper layers of the stratified epithelium of the epidermis and in the root sheaths of hairs. These cells are recognized by their vesicular character and by the fact that they occur most abundantly in the interpapillary portions of the epidermis. The deeper surface of the tactile cell rests in a cup-like expansion of a terminal nerve fibril which is known as the *tactile meniscus.*

Similar tactile cells are found in the hair bulbs. The hair bulbs are important tactile end-organs. The innervation is very complex. The nerves end as: (a), straight parallel fibers; (b) circular fibers; (c) fibers associated with special tactile cells. The hair bulbs mediate protopathic tactile sensibility. .

Neuro-epithelium.—The cells of some types of neuro-epithelium, e.g., the olfactory cells, are true nerve cells; others are modified epithelial cells, in relation to which the nerves terminate by intercellular end-fibrils. The neuro-epithelium of the eye and the ear will be described in the chapters devoted to these organs, that of the gustatory organ forms typical nerve end-organs,·the taste buds.

Taste Buds (Gustatory Organs).—These end-organs appear to be concerned with the special sense of taste. They occur in the stratified epithelium of the base of the tongue, uvula, soft palate and epiglottis. Disse has also found similar struc-

FIG. 183—TACTILE CELLS IN THE EPITHELIUM OF THE GROIN OF A GUINEA-PIG.

a, tactile cell; c, epithelial cell , m, tactile meniscus, at the end of a nerve fibril; n, nerve fiber. Chloride of gold. Highly magnified (Ranvier).

tures in the nasal mucous membrane. They are most abundant on the lateral surfaces of the circumvallate papillae of the tongue and on the walls of the sulci in the foliate papillae which are most highly developed in the rabbit. They are occasionally found on the fungiform papillae of the tongue, where they occur in considerable numbers in fetal life but mostly disappear before birth, and in the lateral walls of the sulci about the circumvallate papillae.

Taste buds are ovoid, ellipsoidal, or spheroidal masses which occupy almost the entire depth of the epithelial layer. Their broad base rests upon the basement membrane, their narrower apex extends nearly·to the surface of the epithelium. The apex of the bud is thus covered by the superficial squamous epithelial cells except for a narrow tubular opening which overlies the superficial pole of the end-organ This canal presents an external and an internal ostium, respectively designated the outer and inner *taste pore.* The inner taste pore leads into a goblet-shaped depression in the apex of the taste bud, into which the cuticular processes of the gustatory cells project. Composite buds with two and three pores are common in the foliate papillae of the rabbit; Heidenhain[1] reports also buds with four, five and six pores.

The taste buds consist essentially of two varieties of cells, the gustatory and the sustentacular The latter include the broad outer sustentacular or tegmental cells at the surface of the bud, the inner sustentacular cells within, and the basal cells which lie near the basement membrane.

[1] Heidenhain, 1914

THE GUSTATORY CELLS.—The gustatory cells are slender neuro-epithelial structures whose nucleus causes a fusiform enlargement near their center or toward the basal end. Their cytoplasm is finely granular; their nucleus stains deeply and is ovoid or rod-shaped. The distal end of the cell carries a delicate, highly refractive cuticular process which projects beyond the apices of the sustentacular cells and as far as the inner taste pore. Their proximal end is often bifid, forked, or so flattened as to form a foot-like extremity which is connected with the basal cells by fine processes. Sapid substances in solution enter the pore and stimulate the taste cells through the hair processes.

SUSTENTACULAR CELLS.—The outer and inner sustentacular cells are elongated epithelioid cells, having an ovoid or spheroidal vesicular nucleus which causes no bulging of the protoplasm, and a coarsely reticular and frequently vacuolated cytoplasm. The distal ends of the cells taper to blunt points which collectively form the lateral wall of a goblet-shaped cavity at the apex of the taste bud. The proximal end is broad, often blunt or serrated, and, like the gustatory cells, it is connected with the basal cells by protoplasmic processes.

THE BASAL CELLS.—The basal cells are flat-

FIG. 184—NERVE ENDINGS IN HAIR FOLLICLE OF DOG.

Gold chloride preparation. (From Barker after Bonnet.)
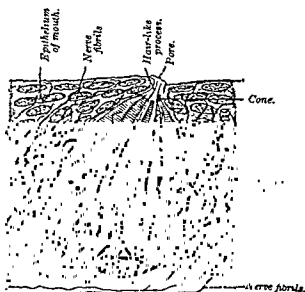
FIG 185—SCHEMATIC REPRESENTATION OF A TASTE BUD.
(After Hermann, from Bohm and von Davidoff.)

tened bodies with small ovoid vesicular nuclei and a relatively small amount of cytoplasm which is prolonged into numerous processes that appear to be continuous with the sustentacular and gustatory cells. These cells have been considered as having a function similar to that of the sustentacular cells.

THE FIBERS.—The nerve fibrils of the taste buds are derived from a subepithelial plexus which distributes terminal fibrils to the gustatory and sustentacular cells (*intragemmal fibers*) and to the intervening portions of the stratified
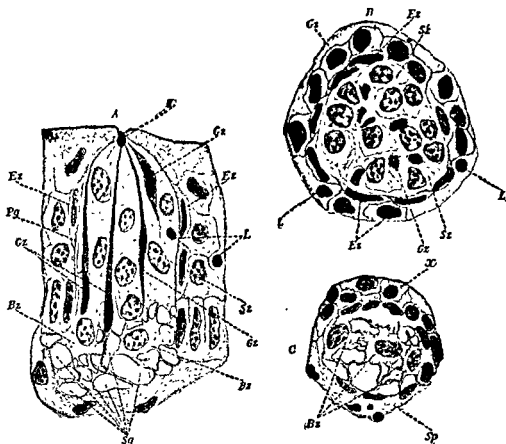
FIG 186—TASTE BUD FROM THE HUMAN TONGUE.

A, in longitudinal section, *B*, transection through the deeper third; *C*, transection through the base. *Bz*, basal cells; *Ez*, extrabulbar cells; *Gz*, gustatory cell; *L*, leukocytes, in *A* one of these is seen in the pore; *Pg*, perigemmal space; *Sg*, subgemmal spaces; *Sp*, connective tissue of the lamina propria; *Sz*, sustentacular cells; *x*, cells of the adjacent epithelium. (Graberg.)

epithelium (*intergemmal fibers*) where they terminate in end-fibrils. Von Lenhossék [2] states that the intragemmal and intergemmal fibers are never derived from the same nerve fiber. *Circumgemmal* fibers, distributed as varicose fibrils to the surface of the taste bud, may, however, arise from the same nerve fiber as the intragemmal branches.

Those nerve fibers which enter the taste buds form fine varicose fibrils which are closely applied to, but are not continuous with, the gustatory and the sustention-

[2] Von Lenhossék, 1892

tacular cells. The terminal twigs of these fibrils end by minute end-knobs which are scarcely distinguishable from the varicosities (Fig. 185).

NERVE ENDINGS IN CONNECTIVE TISSUE

The nerve fibers form extensive plexuses in the connective tissues from which terminal branches are distributed to the epithelium (free sensory endings), the walls of the blood and lymphatic vessels (sympathetic vasomotor endings), and to the numerous sensory end-organs (encapsulated endings) which occur in abun-
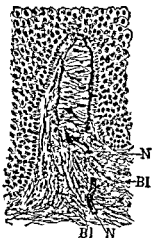
FIG. 187.   FIG. 188.

FIG. 187.—TACTILE CORPUSCLE OF MEISSNER FROM THE SKIN OF THE HUMAN TOE.

Bl, blood vessel; *N*, myelinated nerve fiber. Highly magnified. (Schiefferdecker.)
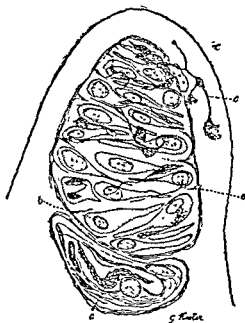
FIG. 188.—TACTILE CORPUSCLE OF MEISSNER.

b, epithelioid cells; *c*, nerve endings; *e*, connective tissue capsule. (Maximow, after Van de Velde.)

dance in most of the connective tissues. Nerves also terminate in connective tissue by free end-fibrils some of which, as in the epithelial tissues, possess minute end-knobs. Free nerve endings of this nature occur in the tendons, the lungs, the stomachal and intestinal mucous membranes, the meninges, and in the superficial layer of the corium of the skin and the hair follicles.

The following types of nerve end-organs are found in connective tissue:

Tactile Corpuscles (Touch Corpuscles of Meissner).—These organs are formed by the terminal expansion of a nerve fiber, which forms a varicose plexus inclosed within a delicate connective tissue sheath. The nerve fiber, or its primary branches, prior to its ultimate division makes several spiral turns about the corpuscle. The course of the nerve fiber gives the corpuscle a peculiar spirally striated appearance. Within the corpuscle the nerve fiber breaks into a plexus of varicose

fibrils, many of which end in knobbed extremities. The corpuscles also contain many flattened or cuneiform epithelioid cells, of *mesodermal origin*, which are interspersed among the nerve fibrils.

Tactile corpuscles occur in largest numbers in the cutaneous *papillae* of the finger tips, where there may be as many as twenty to the square millimeter. They are found in considerable abundance also in other highly sensitive regions, including especially the corium of the toe tips, the lips, nipple, conjunctiva, glans penis and clitoris.

The cutaneous senses comprehend four different qualities of sensation: pressure, warmth, cold and pain. These are mediated by two distinct groups of sensory fibers ending in the skin: the one conveys the impulses for pain and extremes of temperature (protopathic sensibility), the other for light pressure and small changes of temperature (epicritic sensibility). The various subcutaneous endings mediate subcutaneous sensibility to pressure and movement.

FIG 189.—TACTILE CORPUSCLE OF MEISSNER.

a, nerve fibrils which enter the corpuscle and supply its nerve skein Methylene blue. Very highly magnified. (Dogiel)

Ruffini's End-organs.—These bodies, also known as *terminal cylinders*, resemble the tactile corpuscles in structure but possess a definite, though thin, connective tissue sheath within which the terminal arborization of the nerve fiber is embedded in a granular core. They occur in the deeper part of the true skin near its junction with the subcutaneous tissue and in the connective tissue septa of the latter, whereas the tactile corpuscles are found in the papillary layer of the skin. Ruffini states that they occur in large numbers in the skin of the finger tips, where they rival in number the rather more deeply placed pacinian corpuscles

FIG. 190.—RUFFINI'S END-ORGAN.

A single nerve fiber breaks up to form the tangle of nerve fibrils within the organ *gH*, myelin sheath; *il*, terminal fibrils of the axis cylinder; *L*, connective tissue capsule. (Ruffini.)

The Ruffini organs are cylindrical in shape and their nerve fibers usually enter at the side of the organ, though occasionally at its end. Now and then a single branching nerve fiber is distributed to several of these end-organs.

End-bulbs (Krause).—These structures (*bulbous corpuscles*), together with those which follow, form the true so-called *encapsulated nerve end-organs*. In the end-bulbs the nerve forms a terminal arborization of varicose and knobbed fibrils which freely anastomose. The bulb is invested with a distinct connective tissue capsule. On entering the bulb the nerve fiber loses its sheaths and the perineurium, now represented by Henle's sheath, becomes continuous with the capsule of the bulb. Within the capsule the nerve fibrils are embedded in a granular *inner bulb*.

The end-bulbs vary much in both size and shape. They may be either spheroidal, ovoid, twisted or convoluted, branched or compound, or cylindroid. They are found abundantly in the conjunctiva, but also occur in the corium

FIG. 191.—END-BULB OF KRAUSE FROM THE MARGIN OF THE OCULAR CONJUNCTIVA

The axon forms a dense skein within the encapsulated bulb. Methylene blue. Highly magnified. (Dogiel.)

of the skin. Similar, though more highly developed, end-bulbs form the so-called *genital corpuscles* which are found in considerable numbers in the connective tissue of the glans penis, prepuce, and clitoris. In some of the smaller (*cylindrical*) end-

FIG. 192.—GENITAL CORPUSCLES FROM THE CLITORIS OF A RABBIT.

A single axon from the nerve plexus enters each corpuscle. Methylene blue. Highly magnified. (Retzius.)

bulbs found in the tendons, the mucous membranes, and in certain portions of the skin, the nerve fiber fails to divide but ends near the distal extremity of the bulb in a small fusiform end-knob

fibrils, many of which end in knobbed extremities. The corpuscles also contain many flattened or cuneiform epithelioid cells, of mesodermal origin, which are interspersed among the nerve fibrils.

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FIG 189—TACTILE CORPUSCLE OF MEISSNER.

a, nerve fibrils which enter the corpuscle and supply its nerve skein. Methylene blue. Very highly magnified. (Dogiel)

FIG. 190.—RUFFINI'S END-ORGAN.

A single nerve fiber breaks up to form the tangle of nerve fibrils within the organ, *gH*, myelin sheath; *il*, terminal fibrils of the axis cylinder; *L*, connective tissue capsule. (Ruffini)

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FIG. 191.—END-BULB OF KRAUSE FROM THE MARGIN OF THE OCULAR CONJUNCTIVA.

The axon forms a dense skein within the encapsulated bulb. Methylene blue. Highly magnified (Dogiel)

The end-bulbs vary much in both size and shape. They may be either spheroidal, ovoid, twisted or convoluted, branched or compound, or cylindroid. They are found abundantly in the conjunctiva, but also occur in the corium of the skin. Similar, though more highly developed, end-bulbs form the so-called *genital corpuscles* which are found in considerable numbers in the connective tissue of the glans penis, prepuce, and clitoris. In some of the smaller (*cylindrical*) end-
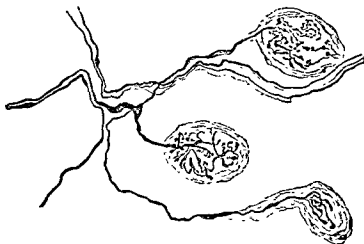
FIG 192.—GENITAL CORPUSCLES FROM THE CLITORIS OF A RABBIT.

A single axon from the nerve plexus enters each corpuscle. Methylene blue. Highly magnified (Retzius.)

bulbs found in the tendons, the mucous membranes, and in certain portions of the skin, the nerve fiber fails to divide but ends near the distal extremity of the bulb in a small fusiform end-knob.

Lamellar Corpuscles (Pacinian Corpuscles, Vater's Corpuscles, Vater-Pacinian Corpuscles.)—These are among the largest of the nerve end-organs. In

FIG. 193—A LAMELLAR CORPUSCLE FROM THE MESENTERY OF A CAT.
A, a nearly axial section; *B*, a transection. ×410.

FIG 194   FIG 195.

FIG 194.—A LAMELLAR CORPUSCLE FROM THE PLEURA OF A CHILD.
a, lamellae; *b*, nerve fiber; *c*, nerve. Methylene blue. Moderately magnified (Dogiel.)

FIG 195.—A LAMELLAR CORPUSCLE FROM THE MESENTERY OF A KITTEN.
The nerve fiber shows lateral processes, many of which are knobbed. Methylene blue. Moderately magnified. (Sala)

the mesentery of the cat they are of macroscopic size, varying in length from two to three millimeters. They assume the form of a large ovoid thickening, placed

upon the end of a nerve fiber. The pacinian corpuscle consists of a thick lamellated connective tissue coat, and a central granular protoplasmic core which is pierced by the nerve fiber. The myelinated nerve fiber enters the axis of the corpuscle, its Henle's sheath becoming continuous with the superficial capsule of connective tissue. The nerve fiber on entering the core loses its myelin sheath, and after traversing a greater or less portion of the core divides into two to five branches which end near the distal pole in a disk-like expansion. In its course through the core, the nerve fiber gives off fine lateral twigs. The basal pole of the corpuscle receives also one or several minute muscular blood vessels. These end in a capillary network between the lamellae.

The connective tissue sheath consists of a granular protoplasm which is permeated by densely felted spiral fibers and is divided into ten to fifty concentric lamellae by lines of flattened connective tissue cells and fibers. According to Schwalbe, however, these cells form an endothelioid coat on either surface of each lamella. Lamellar corpuscles are occasionally compound, two or more adjacent corpuscles being supplied by branches of the same nerve fiber.

Lamellar corpuscles are found in large numbers in the subcutaneous tissue of the finger tips and of the penis, as well as in the skin of other parts, in the mesentery and the connective tissue of the neighboring organs, e.g., the pancreas, in the prevertebral connective tissue of the abdomen and mediastinum, near the walls of the large blood vessels, in the serous membranes (pleura, pericardium, peritoneum), in the periarticular connective tissue and periosteum, in the sheaths of the larger nerve trunks, and in the connective tissue of the thyroid gland and of the skeletal muscles They function as pressure and strain receptors, mediating deep sensibility and joint sensibility. Certain investigators interpret them also as regulators of blood pressure.

FIG. 196—A LAMELLAR CORPUSCLE IN LONGITUDINAL SECTION, SHOWING A NETWORK OF SPIRAL ELASTIC FIBERS.

Weigert's elastic tissue stain. Highly magnified. (Sala.)

The Corpuscles of Herbst (Key-Retzius Corpuscles).—The corpuscles of Herbst are similar in structure to the lamellar corpuscles except that the core which surrounds the axial nerve fiber contains cuboidal *tactile cells*. They occur only in the cere of aquatic birds.

The Corpuscles of Grandry (Merkel's Corpuscles).—The corpuscles of Grandry, also found only in aquatic birds, contain several tactile cells of ectoblastic origin similar to those found in the epidermis. Each cell is in relation with a ring or meniscus formed by the expanded end of a nerve fiber. The whole is

Lamellar Corpuscles (Pacinian Corpuscles, Vater's Corpuscles, Vater-Pacinian Corpuscles.)—These are among the largest of the nerve end-organs. In

FIG. 193.—A LAMELLAR CORPUSCLE FROM THE MESENTERY OF A CAT.

A, a nearly axial section; *B*, a transection. ×410.

FIG. 194.   FIG. 195

FIG 194.—A LAMELLAR CORPUSCLE FROM THE PLEURA OF A CHILD.

a, lamellae; *b*, nerve fiber; *c*, nerve. Methylene blue. Moderately magnified. (Dogiel.)

FIG. 195.—A LAMELLAR CORPUSCLE FROM THE MESENTERY OF A KITTEN.

The nerve fiber shows lateral processes, many of which are knobbed. Methylene blue. Moderately magnified. (Sala)

the mesentery of the cat they are of macroscopic size, varying in length from two to three millimeters. They assume the form of a large ovoid thickening, placed

upon the end of a nerve fiber. The pacinian corpuscle consists of a thick lamellated connective tissue coat, and a central granular protoplasmic core which is pierced by the nerve fiber. The myelinated nerve fiber enters the axis of the corpuscle, its Henle's sheath becoming continuous with the superficial capsule of connective tissue. The nerve fiber on entering the core loses its myelin sheath, and after traversing a greater or less portion of the core divides into two to five branches which end near the distal pole in a disk-like expansion. In its course through the core, the nerve fiber gives off fine lateral twigs. The basal pole of the corpuscle receives also one or several minute muscular blood vessels. These end in a capillary network between the lamellae.

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Fig. 196.—A Lamellar Corpuscle in Longitudinal Section, Showing a Network of Spiral Elastic Fibers.

Weigert's elastic tissue stain. Highly magnified. (Sala.)

The Corpuscles of Herbst (Key-Retzius Corpuscles).—The corpuscles of Herbst are similar in structure to the lamellar corpuscles except that the core which surrounds the axial nerve fiber contains cuboidal *tactile cells.* They occur only in the cere of aquatic birds.

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included within a thin connective tissue capsule and may be regarded as a *compound tactile cell* occurring in connective tissue.

The Golgi-Mazzoni Corpuscles.—The Golgi-Mazzoni corpuscles described by Ruffini[a] somewhat resemble the pacinian corpuscles in that they possess a lamellar,

FIG. 197.   FIG. 198.

FIG. 197.—AXIAL SECTION OF A CORPUSCLE OF HERBST FROM A DUCK'S BILL

a, myelinated nerve fiber; *b*, naked axial nerve fiber with a bulbous end; *c*, nuclei of the core; *d*, inner concentric capsule; *e*, nuclei of the outer lamellated capsule. ×380 (Sobotta.)

FIG. 198.—A PAPILLA OF THE DUCK'S TONGUE CONTAINING A CORPUSCLE OF GRANDRY.

The corpuscle contains four large cells, between which are the tactile menisci of the nerve ending. *n*, nerve. Highly magnified. (After Merkel, from Kölliker.)

though relatively very thin, connective tissue sheath and a central granular core. The core, however, is relatively excessive in size, and the entering nerve fiber breaks into a number of branches with discoid terminal expansions similar to those found in the nerve endings of Golgi in the tendons. They occur in the corium of the skin in certain regions (*e.g.*, the external genitalia, finger tips), and in the conjunctiva and the periosteum.

NERVE ENDINGS IN MUSCLE AND TENDON

VOLUNTARY STRIPED MUSCLE

Motor End-plates.—These organs form the intramuscular endings of motor axons whose cell bodies are found in the ventral horns of the gray matter of the spinal cord. The efferent fibers reach the muscle through the many cerebrospinal nerve trunks. On entering the muscle these nerves form a plexus in the perimysium

[a] Ruffini, 1894.

from which nerve fibers are distributed within the muscle bundles. Here they form
an abundant plexus of branching nerve fibers within the endomysium, the ulti-
mate branches being of sufficient number to supply one or more terminal nerve
fibers to each muscle fiber.

FIG 199—GOLGI-MAZZONI CORPUSCLES FROM THE SUBCUTANEOUS TISSUE OF THE TIP
OF THE FINGER

(Ruffini)

At the surface of the muscle fiber the nerve fiber loses its myelin sheath, its
neurilemma becomes continuous with the sarcolemma of the muscle cell, and its
naked axis cylinder divides into two to five branches, which end, often after
repeated subdivision, in flattened terminal disks, distributed in mammals over a
limited, in amphibians over a broad area, but which never completely encircle the
cylindrical muscle cell.

included within a thin connective tissue capsule and may be regarded as a *compound tactile cell* occurring in connective tissue.

The Golgi-Mazzoni Corpuscles.—The Golgi-Mazzoni corpuscles described by Ruffini[3] somewhat resemble the pacinian corpuscles in that they possess a lamellar,

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a, myelinated nerve fiber; *b*, naked axial nerve fiber with a bulbous end; *c*, nuclei of the core; *d*, inner concentric capsule; *e*, nuclei of the outer lamellated capsule. ×380. (Sobotta.)

FIG. 198—A PAPILLA OF THE DUCK'S TONGUE CONTAINING A CORPUSCLE OF GRANDRY.

The corpuscle contains four large cells, between which are the tactile menisci of the nerve ending *n*, nerve. Highly magnified. (After Merkel, from Kölliker.)

though relatively very thin, connective tissue sheath and a central granular core. The core, however, is relatively excessive in size, and the entering nerve fiber breaks into a number of branches with discoid terminal expansions similar to those found in the nerve endings of Golgi in the tendons. They occur in the corium of the skin in certain regions (*e.g.*, the external genitalia, finger tips), and in the conjunctiva and the periosteum

NERVE ENDINGS IN MUSCLE AND TENDON

VOLUNTARY STRIPED MUSCLE

Motor End-plates.—These organs form the intramuscular endings of motor axons whose cell bodies are found in the ventral horns of the gray matter of the spinal cord. The efferent fibers reach the muscle through the many cerebrospinal nerve trunks. On entering the muscle these nerves form a plexus in the perimysium

[3] Ruffini, 1894.

from which nerve fibers are distributed within the muscle bundles. Here they form an abundant plexus of branching nerve fibers within the endomysium, the ultimate branches being of sufficient number to supply one or more terminal nerve fibers to each muscle fiber.

FIG 199—GOLGI-MAZZONI CORPUSCLES FROM THE SUBCUTANEOUS TISSUE OF THE TIP OF THE FINGER.

(Ruffini.)

At the surface of the muscle fiber the nerve fiber loses its myelin sheath, its neurilemma becomes continuous with the sarcolemma of the muscle cell, and its naked axis cylinder divides into two to five branches, which end, often after repeated subdivision, in flattened terminal disks, distributed in mammals over a limited, in amphibians over a broad area, but which never completely encircle the cylindrical muscle cell.

The terminal expansions of the axon rest upon a granular, slightly raised *sole plate* which contains many ovoid muscle nuclei, the *sole nuclei*.

Muscle Spindles (Neuromuscular Spindles, Neuromuscular End-organs).— These are *sensory nerve endings* which are concerned with the so-called muscle sense. They are especially numerous in the extrinsic muscles of the tongue, in the small muscles of the hand and foot, and in the intercostal muscles.[4] They have

FIG 200—MOTOR NERVE ENDINGS IN STRIATED MUSCLE.

A, from a lizard; *B*, from the guinea-pig; *C*, from the hedge-hog *A* and *C* are surface views; in *B* the end-plate is seen in profile. *a*, muscle fiber; *b*, nerve fiber; *c*, nerve ending in the form of a brush, *d*, the sole plate; *e*, sarcolemma. *A*, ×160; *B*, ×700; *C*, ×1200 (Böhm and von Davidoff.)

not been found in the muscles of the diaphragm. A detailed description of the developing neuromuscular spindle in the extrinsic eye muscles of the pig has been given by Sutton.[5] He describes a coarsely granular "plaque," different from both muscle and nerve, which he inclines to regard as an intermediary structure perhaps a *receptor substance* analogous to the sole plate of motor endings.

A muscle spindle contains from five to twenty striated muscle fibers of small size, and an almost equal number of nerve fibers. The whole is inclosed within a connective tissue capsule of considerable thickness. The bundle of *intrafusal muscle fibers* is again surrounded by a delicate *axial sheath* of connective tissue

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4 Huber, 1902.
5 Sutton, 1915.

which is united to the capsule by bands of fine fibrous tissue which span the broad *periaxial lymphatic space*. The larger of these fibrous bands support the nerve fibers, on their way to the intrafusal muscle cells, together with several small blood vessels.

The muscle spindles form long fusiform bodies (from 1 to 5 millimeters in length) whose muscle fibers at the pole of the spindle may be connected with the tendon, or they may join other muscle fiber bundles. The muscle spindles are usually found in the fibrous septa of the perimysium. Compared with the adjacent muscle fibers, the intrafusal fibers have a smaller diameter, are less distinctly but more coarsely striped, and contain some centrally located nuclei.

Either one or several nerve trunks enter the spindle, usually near its equator rather than at its poles. The nerve fibers branch repeatedly in the intracapsular connective tissue, and finally pierce the axial sheath as naked processes which form a rich arborization of terminal fibrils about the intrafusal muscle fibers. Ruffini distinguishes three types of terminal nerve fibrils: (1) *annular*, which form rings about the muscle fibers; (2) *spiral*, which are spirally twisted about the intrafusal fibers, and (3) *dendritic branchings*, in which the axons break into numerous irregular processes with laminate expansions.

Fig. 201.—A MUSCLE SPINDLE FROM THE PSOAS MAGNUS OF MAN.

1, intrafusal muscle fibers; *2*, nerve fibers; *3*, axial sheath; *4*, connective tissue capsule; *5*, muscle fibers of an adjacent fasciculus; *6*, periaxial lymphatic spaces; *7*, blood vessel. Hematein and eosin. ×470.

Motor end-plates for the muscle fibers of the spindle as well as sympathetic vasomotor nerves for its blood vessels have also been demonstrated within the muscle spindles.

That the muscle spindles are sensory and not motor organs has been demonstrated by Sherrington,[6] who found that they were not affected by the muscular atrophy following section of the peripheral motor neurons, and by Horsley[7] and others who have found that the muscle spindles are *unaffected in* cases of extreme muscular atrophy in man.

Neurotendinous End-organs (Golgi End-organs, Tendon Spindles).—These organs occur in the tendons of muscles near the junction of the tendon bundles with the muscle fibers. They are fusiform in shape and consist of a thin lamellar capsule of connective tissue which incloses several intrafusal tendon bundles of dense fibrous tissue. A narrow lymphatic space intervenes between the capsule and the intrafusal tendon bundles.

Nerve fibers enter the spindle and give off several myelinated branches which

[6] Sherrington, 1894
[7] Horsley, 1897.

The terminal expansions of the axon rest upon a granular, slightly raised *sole plate* which contains many ovoid muscle nuclei, the *sole nuclei.*

Muscle Spindles (Neuromuscular Spindles, Neuromuscular End-organs).— These are *sensory nerve endings* which are concerned with the so-called muscle sense. They are especially numerous in the extrinsic muscles of the tongue, in the small muscles of the hand and foot, and in the intercostal muscles.[4] They have

FIG 200.—MOTOR NERVE ENDINGS IN STRIATED MUSCLE.

A, from a lizard; *B*, from the guinea-pig; *C*, from the hedge-hog. *A* and *C* are surface views; in *B* the end-plate is seen in profile. *a*, muscle fiber; *b*, nerve fiber; *c*, nerve ending in the form of a brush; *d*, the sole plate; *e*, sarcolemma. *A*, ×160; *B*, ×700; *C*, ×1200. (Bohm and von Davidoff.)

not been found in the muscles of the diaphragm. A detailed description of the developing neuromuscular spindle in the extrinsic eye muscles of the pig has been given by Sutton.[5] He describes a coarsely granular "plaque," different from both muscle and nerve, which he inclines to regard as an intermediary structure perhaps a *receptor substance* analogous to the sole plate of motor endings.

A muscle spindle contains from five to twenty striated muscle fibers of small size, and an almost equal number of nerve fibers. The whole is inclosed within a connective tissue capsule of considerable thickness. The bundle of *intrafusal muscle fibers* is again surrounded by a delicate *axial sheath* of connective tissue

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[4] Huber, 1902
[5] Sutton, 1915.

CLASSIFICATION OF NERVE END-ORGANS IN ACCORDANCE WITH SHERRINGTON'S TERMINOLOGY

NERVE END-ORGANS
(a) Receptors
(b) Effectors

I. Somatic Receptors

A. Exteroceptors
1. Pressure receptor ...... (Deep sensibility) — (Pacinian corpuscle, and similar encapsulated end-organs)
2. Touch receptor ...... (Cutaneous sensibility)
   - (a) Epicritic (Meissner's corpuscle)
   - (b) Protopathic (nerve endings in hair bulbs)
3. Cold receptor ...... — End-bulb of Krause
4. Heat receptor ...... — "Genital corpuscle," and similar corpuscles
5. Pain receptor ...... — Free nerve endings in epidermis
6. Sound (noise and tone) receptor (Spiral organ of Corti of ear)
7. Light (ether wave) receptor ...... (Retina of eye)
8. Odor receptor ...... (Olfactory mucosa *both exteroceptive and interoceptive*)

B. Proprioceptors
1. End-organ of muscular sensibility (muscle spindle)
2. End-organ of tendon sensibility (tendon spindle)
3. End-organ of joint sensibility (pacinian corpuscle)
4. Organs of static and equilibratory sensation (utricle, saccule and semicircular ducts of ear)

II. Visceral Receptors (Interoceptors)

A. General interoceptors; e.g., organs of hunger, thirst, sex, visceral pain, etc. (free nerve endings in mucous membrane)

B. Special interoceptors
1. Organs of taste (taste buds, and free nerve endings in tongue)
2. Organs of smell (olfactory cells of nose)

III. Somatic Effectors

Motor end-plates of voluntary striped muscle

IV. Visceral Effectors

A. Free nerve endings in cardiac and smooth muscle
B. Free nerve endings in glands

run between the tendon bundles near the axis of the spindle. These finally form naked end fibrils with branching end plates, which surround the tendon bundles in an annular or spiral manner.[8] Since the structure of the Golgi tendon spindles
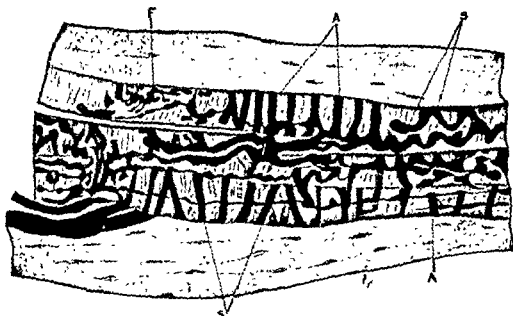
Fig. 202—Middle Third of a Terminal Plaque in the Muscle Spindle of an Adult Cat.

A, rings; *F*, dendritic branchings; *S*, spirals Chloride of gold preparation. Highly magnified. (Ruffini.)
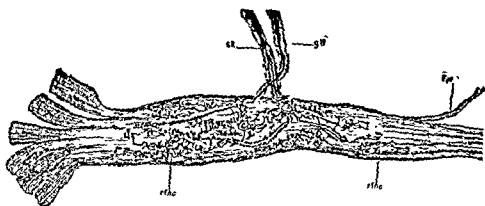
Fig 203—Neurotendinous End-organ or Tendon Spindle of Golgi.

fpt, bundle of tendon fibers, *gH*, myelinated nerve fiber; *rfne*, ribbon-like terminal ramifications of the axon, *SR*, node of Ranvier. Moderately magnified. (Ciacio.)

closely resembles that of the muscle spindles, they are probably of similar function.

Pacinian Corpuscles and End-bulbs of Krause.—In addition to the special motor and sensory end-organs described above, pacinian corpuscles and end-bulbs of Krause are also found in the connective tissue of striated muscles.

[8] Ciacio, 1891.

CLASSIFICATION OF NERVE END-ORGANS IN ACCORDANCE WITH SHERRINGTON'S TERMINOLOGY

NERVE END-ORGANS
(a) Receptors
(b) Effectors

I Somatic Receptors

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   (a) Epicritic (Meissner's corpuscle)
   (b) Protopathic (nerve endings in hair bulbs)
   End-bulb of Krause
   "Genital corpuscle," and similar corpuscles
   Free nerve endings in epidermis
3 Cold receptor ....
4 Heat receptor ....
5. Pain receptor ....
6 Sound (noise and tone) receptor...(Spiral organ of Corti of ear)
7 Light (ether wave) receptor ......(Retina of eye)
8 Odor receptor ......(Olfactory mucosa *both exteroceptive and interoceptive*)

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III. Somatic Effectors

Motor end-plates of voluntary striped muscle

IV. Visceral Effectors

A. Free nerve endings in cardiac and smooth muscle
B. Free nerve endings in glands

End-plates of "accessory" unmyelinated, probably sympathetic, fibers have also been described in striped muscle.[9, 10] Muscle tonus is believed to depend upon this innervation (Fig. 131). The large body of evidence, both histologic and experi-

FIG 204.—NERVE ENDINGS IN CARDIAC MUSCLE FROM THE HEART OF A CAT.

a, muscle fiber; *b*, nerve fiber. Methylene blue. Highly magnified. (Huber and De Witt.)

mental, for and against the occurrence of a hypolemmal sympathetic innervation of skeletal muscle, has been critically analyzed by Hinsey.[11] He interprets the evidence as favoring the negative position that the sympathetic nerves in skeletal muscle are extralemmal and supply only the blood vessels. Similarly, he regards the weight of evidence as opposed to the view that the sympathetic system controls postural tonus, as distinct from the contractile tonus which is mediated by the somatic motor innervation.

CARDIAC AND SMOOTH MUSCLE

The nerves (sympathetic) of the heart are distributed to the cardiac ganglia, whence unmyelinated fibers pass to all portions of the organ and form a very rich plexus in the intermuscular connective tissue. Fine terminal fibrils are dis-

FIG. 205—NERVE ENDINGS IN SMOOTH MUSCLE, FROM THE INTESTINE OF A CAT.

a, muscle cell; *b*, nerve fiber. Methylene blue. Highly magnified. (Huber and De Witt.)

tributed from this plexus to the muscle fibers, upon whose surface they end in varicose swellings and end-knobs. While most of these fibrils are probably motor in function, others which end in the intermuscular connective tissue are more probably afferent (sensory). Occasional endings in cardiac muscle resemble the simpler motor end-organs of skeletal muscle.

In smooth muscle, plexuses of sympathetic nerve fibers occur in the intervals between the bundles of muscle cells. Secondary plexuses of naked fibrils are found among the muscle cells, and from this plexus fine lateral fibrils are distributed to the muscle cells, upon whose surface they end in small terminal granules or end-knobs Many of the nerve fibers in smooth muscle are undoubtedly of sensory function.

The immediate motor stimulus to cardiac and smooth muscle function is be-

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9 Perroncito, 1903.
10 Boeke, 1913.
11 Hinsey, 1934.

lieved to be the adrenalin set free at the visceral terminals of the sympathetic neurons.[12]

The nerve endings and the distribution of the peripheral nerve fibers in the various organs of the body are more fully described in the several chapters devoted to those organs.

The table on page 165 gives the classification of nerve end-organ in Sherrington's terminology.

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[12] Cannon, 1939.

CHAPTER VII

THE BLOOD VASCULAR SYSTEM

This system includes the heart, arteries, capillaries and veins. These structures form a continuous set of branching tubes, which convey the blood from the heart, through the arteries and capillaries, and back again through the veins to the heart. In the capillaries a portion of the blood plasma transudes into the tissue spaces, where it forms the tissue juices, and from which it is returned to the blood by the lymphatic vessels, the terminal branches of which empty into the subclavian veins.

This entire vascular system is completely lined by a single layer of flattened epithelial cells, the *endothelium*. The cells are united edge to edge by an intercellular cement substance, to form a continuous membrane throughout the entire system. The blood vessels include the arteries, capillaries, and veins, and these, together with the heart, will form the subject of the present chapter. The lymphatic vessels (lymph vascular system) will be described in connection with the lymphatic system. The blood and lymph vessels together with their contents comprise the *vascular tissue*.

ARTERIES

The arteries convey the blood from the heart to all the tissues of the body. They are therefore almost universally present, but vary in size from the aorta down to minute unnamed vessels of microscopic caliber. They are divisible, according to size, into the large, medium-sized, and small arteries, the arterioles, and what may be termed the arterial capillaries, or precapillary arteries. The large arteries include only the aorta and the largest of its immediate branches (innominate, common carotids, subclavians and common iliacs), and the pulmonary artery—the conducting arteries; the medium-sized (distributing) arteries comprise nearly all the remaining named arteries of the body; small arteries, arterioles, and precapillary arteries include those unnamed arteries which are to be found in nearly all of the organs and tissues of the body.

Medium-sized Arteries.—A medium-sized artery will be described first, as presenting the typical arterial structure Such a vessel consists of three coats: the internal coat (tunica intima, or interna), the middle coat (tunica media), and the external coat (tunica adventitia, or externa).

The internal coat, *tunica intima*, presents three layers, the innermost being

tissue usually predominates, but in the larger arteries elastic tissue is so abundant as to appear quite in excess of the muscular; in the smaller arteries, however, the muscular tissue is by far the more abundant.

The smooth muscle cells (fibers) are circularly disposed in the wall of the vessel; they are short, of irregularly serrated outline, and are intimately united with one another. Quite frequently the muscle fibers possess short branches which interdigitate with those of neighboring fibers. In the larger vessels they are arranged in layers which alternate with the sheets of elastic tissue. Small bundles of longitudinal smooth muscle fibers are occasionally found in the outer portion of the tunica media.
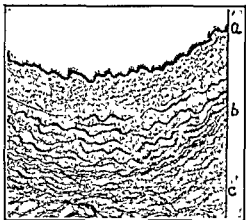
FIG. 207 —THE EXTERNAL CAROTID ARTERY OF A CHILD.

a, tunica intima, the internal elastic membrane is prominent; b, tunica media, containing smooth muscle and several wavy layers of elastic tissue; c, tunica adventitia, containing many transversely and obliquely cut elastic fibers and much wavy connective tissue. (Magrath)

The elastic tissue of the middle coat is disposed in membranous sheets which, in the larger vessels, are embedded in a fine fibrillar connective tissue. In these vessels, also, the fibro-elastic membranes thus formed alternate with the layers of smooth muscle, throughout the entire thickness of the tunica media. In consequence of the relaxation of the normal arterial tone and the contraction of the muscular wall in rigor mortis, as seen in the usual preparations, these elastic layers, as well as the internal elastic membrane, are thrown into wavy folds.

The external coat, tunica adventitia, consists chiefly of fibrous connective tissue. Relatively few elastic fibers occur in this coat, and these for the most part lie in its inner portion, adjoining the tunica media. In the larger arteries, when especially abundant, the elastic fibers form an incomplete layer, which may be termed the external elastic membrane. Like the internal elastic membrane, this layer might well be considered as belonging to the tunica media, of which coat it would then form the outermost stratum.

The collagenous fibers of the tunica adventitia are disposed in dense interlacing bundles, to form a firm, unyielding coat. At the periphery of the artery the connective tissue bundles of the adventitia intermingle with those of the adjacent areolar connective tissue, in which the blood vessels are nearly always embedded, hence the outer boundary of this coat is usually more or less ill defined.

The fibrous bundles of the adventitia are disposed somewhat obliquely or diagonally about the artery, thus forming a closely felted connective tissue network. Small nutrient blood vessels, both arteries and veins (vasa vasorum), and minute nerve trunks with occasional ganglia, occur in this coat. From these vasa et nervi vasorum capillaries and fine nerve fibers, both sensory and autonomic vasomotor, are distributed to the muscular coat. No blood vessels are found in

the tunica intima. In the larger vessels the adventitia may contain also an occasional lamellar corpuscle. The adventitia contains abundant perivascular lymphatics. Nervi vasorum are said to be lacking in the blood vessels of the brain and spinal cord. Vasa vasorum occur only in vessels of more than 1 mm. diameter and are said to be lacking in the blood vessels of the heart.

General Characteristics of the Arterial Wall.—The tunica media is almost invariably the thickest of the arterial coats. In the medium-sized vessels, e.g., the

iliac arteries, the adventitia is often of nearly equal thickness, but in the smaller vessels it is much thinner. The arterial wall as a whole, also, is very thick as compared with the lumen of the vessel, and is much thicker than that of a vein of corresponding size.

The wall of the larger arteries is relatively thinner as compared with the lumen than is the case with the arterioles; in the latter vessels the thickness of the arterial wall often exceeds the diameter of their lumen. In certain small arteries, e.g., those of the liver, even this ratio may be exceeded.

The arterial wall contracts firmly in rigor mortis, hence the arteries after death contain but little blood, and because of the density of the tissues which compose their wall, these vessels retain, as a rule, their cylindrical form.

Large Arteries.—The largest arteries differ from the medium-sized type in the excess of elastic tissue and relative deficiency of muscle in their media, the extreme thinness of their adventitia, and the relative thinness of their wall, as a whole, when compared with their lumen. Elastic tissue is especially abundant in all of these vessels; in the media it equals in volume the muscular tissue, in the adventitia it forms a dense network of elastic fibers. In the aorta and the pulmonary artery the elastic tissue surpasses the muscular in the media. These vessels lack a distinct internal and external elastic membrane. The adventitia of the largest arteries is extremely thin, that of the thoracic aorta being not much thicker than its fibrous tunica intima; this coat, therefore, forms but a small portion of the vascular wall in vessels of this type.

FIG. 208.—TRANSVERSE SECTION THROUGH THE WALL OF THE HUMAN DESCENDING AORTA.

I, tunica intima; M, tunica media; A, tunica adventitia. The coarse elastic membranes of the media are conspicuous against the lighter fibromuscular background. ×100

Small Arteries.—In the small arteries the elastic tissue is relatively decreased and the smooth muscle noticeably increased. The tunica intima of these vessels is thin, and is limited externally by an internal elastic membrane, which stands

out prominently because of the relative deficiency of elastic tissue in the tunica media.

In the tunica media of these vessels the plates of elastic tissue which characterize the larger arteries are scarcely to be found. This coat in the small arteries contains very little tissue other than smooth muscle.

The external elastic membrane is indistinct, and the adventitia is not more than one-half to two-thirds as thick as the tunica media.
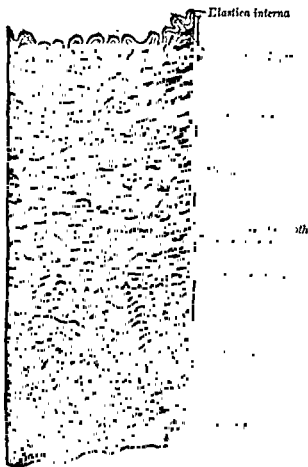
FIG 209—PART OF A CROSS-SECTION OF THE FEMORAL ARTERY OF A DOG.
×150. (From Szymonowicz-MacCallum, *Histology and Microscopic Anatomy*)

Arterioles.—The *arterioles* possess a relatively thicker wall than any other vessel of the arterial system. Their tunica intima is thin, but little fibrous tissue being contained within it, and the internal elastic membrane is represented only by a very incomplete layer of elastic fibers. The tunica media of the arteriole forms two-thirds to three-fourths of its wall, and consists almost entirely of firmly united smooth muscle fibers The adventitia, much thinner than the media, contains bundles of collagenous fibers and delicate interlacing elastic fibrils.

Precapillary Arteries.—The smallest arterioles pass into what may be termed the *precapillary arteries.* In these minute vessels the wall consists of scarcely more than the endothelial lining, about which is an incomplete layer of circular muscle fibers, interspersed with occasional collagenous and elastic fibers. On approaching the capillaries the endothelial tube is gradually laid bare. It is the smooth muscle which is the last of the tissues to disappear from the arterial wall, whereas beyond the capillaries it is the fibrous tissues which are first added to the endothelial tube to form the wall of the smallest venules (Fig. 220).

Atypical Arteries.—Certain atypical arteries differ markedly from the typical structure above described.

The *umbilical arteries* are almost exclusively muscular, and practically lack elastic tissue. The muscle is arranged in two distinct layers: an inner longitudinal, and a wide outer circular; external to these is usually a more or less complete third layer of scattered bundles of longitudinally arranged smooth muscle cells. The umbilical vein is very similar but contains more elastic fibers, and a distinct internal elastic membrane.

The cerebral and meningeal arteries have very thin walls and, exclusive of a relatively very well developed internal elastic membrane, contain but little elastic tissue.

Fig 210—Small Area of Fenestrated Membrane of Henle, Teased from Human Aorta.

F, fenestra; *Pl,* coarser plexus of elastic fibers spread and adherent upon *M,* the fenestrated membrane proper (After M. B. Dees, *Anat. Rec.,* 1923, 26.)

The common iliac, splenic, renal, superior mesenteric and dorsalis penis contain scattered longitudinal bundles of muscle in the media next the intima.

In the *pulmonary arteries* the media is exceptionally well developed. This is the case to an extreme degree in the pulmonary arterioles of the cat. The pulmonary arteries and veins are very similar in structure. In the guinea-pig and opossum the media of the arterioles consists throughout of thick oval segments of circularly disposed smooth muscle alternating with narrow intervals where the muscle layer is relatively thin. In the ox such segmented condition of the media is modified in that the segmentation is spirally disposed.

The media of the roots of the aorta and the pulmonary artery consists largely of cardiac muscle.

In the subclavian artery the longitudinal surpasses the circular muscle in the media. In the arch of the aorta and in the upper portion of the descending aorta longitudinal muscle bundles are found in the intima, media and adventitia (von Bardeleben) The common carotid, common iliac and common femoral (curalis) contain both longitudinally and spirally arranged muscle fibers in the

media. In general, where large arteries are subjected to bendings the circular muscle fibers are reinforced by oblique (spiral) and longitudinal bundles in the media. This is conspicuously the case in the common iliac, the popliteal, and the brachial arteries.[1]
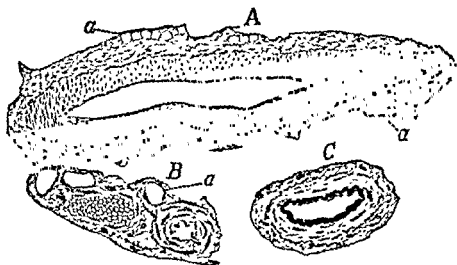
FIG. 211.—A GROUP OF SMALL BLOOD VESSELS.

A, small artery obliquely cut; *B*, arteriole and venule, the latter filled with blood; *a*, fat cells. *A* and *B* are from the connective tissue of the anterior cervical region. Hematein and eosin. *A*, ×110; *B*, ×550. *C*, a small artery near the descending aorta of man; the internal and external elastic membranes are rendered distinct by the stain. Hematein, Weigert's elastic tissue stain, and picrofuchsin, ×550

Comparison of Large and Small Arteries.—The larger arteries are typically elastic, the smaller typically muscular. In the larger arteries the elastic tissue forms about one-half of the entire wall; toward the smaller arteries this tissue progressively diminishes until, in the arterioles, it is limited to an incomplete internal elastic membrane, the homologue of the complete elastic coat or fenestrated coat of Henle, which is found only in larger vessels.

The smooth muscle, on the other hand, increases in *relative* amount from the larger to the smaller arteries. While in the largest vessels it forms not more than one-third, in the arterioles it represents about three-fourths of the arterial wall.

In the largest arteries the adventitia is relatively very thin. That of the medium-sized vessels is much thicker, and the ratio of connective tissue as found in the wall of these vessels remains fairly constant down to the arterioles. In the wall of the precapillary arteries connective tissue is very scanty.

In the aorta all the muscle cells are intimately connected with the elastic membranes. Such "extensor" muscle cells, for the most part arranged obliquely, occur in progressively smaller amount as far as the arterioles. Such mechanism of end-to-end fusion between muscle and elastic fiber provides for regulatory variations in tension of the wall, coincident with changes in blood volume and blood pres-

[1] MacCordick, 1913.

sure, without alteration of the caliber of the lumen. It mediates also the "force-pump" action of the aorta and its larger branches during cardiac diastole.[2]

The capillaries are minute tubes, 5 to 13 μ in diameter, which, in nearly all the tissues of the body, connect the arteries with the veins. Their wall is formed by a layer of endothelial cells which on the one hand is continuous with the endothelial lining of the arteries, on the other hand with that of the veins.
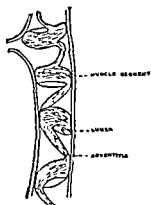
FIG 212   FIG. 213.

FIG 212—A SMALL BRANCH OF PULMONARY ARTERY OF OX.

(Piana) ×70
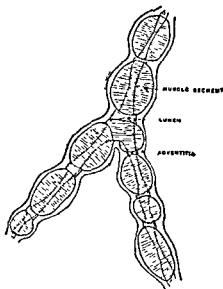
FIG 213—DIVIDING SMALL BRANCH OF PULMONARY ARTERY OF GUINEA-PIG.

Pulmonary arterioles of opossum are almost identical ×50

As a rule there are neither muscle cells nor connective tissue in the wall of the true capillaries; occasionally, however, very fine isolated circumferential elastic fibers encircle the endothelial tube. In the minute arterioles and venules, which are about to terminate in or take origin from the true capillaries and which have been described as precapillary arterioles and venules, a very thin layer of muscle fibers or of connective tissue is added to the endothelial wall of the capillary. On the arterial side the muscle is the first tissue to be thus added, on the venous side the fibrous connective tissue is the first to appear.

The endothelium of the capillary wall consists of flattened plate-like cells which are joined edge to edge by cement substance These cells are somewhat elongated in the axis of the vessel, the shape of the cell, as in the arteries and veins, depending upon the size of the vessel—the smaller the vessel the more elongated its endothelial cells (Fig 46). The margins of these cells are extremely irregular, hence they present a wavy or serrated outline.

[2] Benninghoff, 1927.

Although the endothelial cells of the capillary wall appear to be firmly united to one another, yet they are capable of being separated sufficiently to permit the ready passage of white blood cells through the capillary wall, by diapedesis. The capillary wall does not appear to be an inactive factor in this process, for inert pigment granules may also penetrate the wall of these vessels, the endothelial cells immediately closing the aperture which is thus formed. Nevertheless
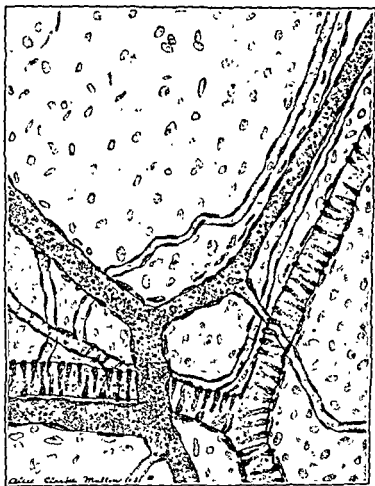
FIG. 214—VIEW OF AN ARTERIOLE AND VENULE WITH PRECAPILLARY AND CAPILLARY BRANCHES.

From the mesentery of cat, toto mount, borax carmine stain.

purely mechanical means, *e.g.*, increased blood pressure, appear also to favor this process. The openings which are formed between the endothelial cells by diapedesis of blood cells are very transitory; they are almost immediately closed by the activity of the endothelium. Such transitory breaches of the capillary wall are termed *stigmata*.

According to Krogh[3] and Vimtrup[4] there are associated with the outer wall

3 Krogh, 1922
4 Vimtrup, 1922.

of the capillaries, in amphibia, mammals and man, scattered elongate muscle cells with numerous irregular processes partially encircling the vessel, the so-called
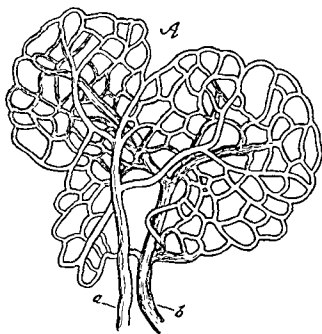
FIG 215.—CAPILLARY NETWORK WITH POLYGONAL MESH IN ADIPOSE TISSUE.

a, afferent artery, b, efferent vein; A, capillary rete. (Redrawn from Ellenberger and v. Schumacher)
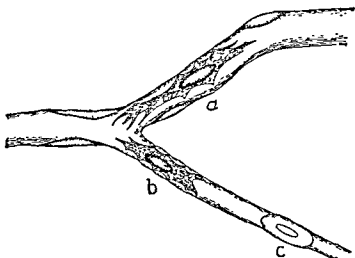
FIG 216.—TWO ROUGET CELLS (a AND b) AS SEEN ON CAPILLARIES IN LIVING NEWT LARVAE. b is contracting, c, is a red corpuscle ×500. (Vimtrup.)

cells of Rouget ('74). Alterations in the caliber of the capillaries are believed to be effected largely through the contractile function of these adventitial muscle cells However, Clark and Clark [5] have shown that the capillary endothelium of

_____

[5] Clark, E. R., and Clark, E. L., 1935.

amphibian larvae has a definite tonicity and is capable of contraction and expansion entirely independent of the presence of any form of periendothelial cell.

The capillaries branch and anastomose with one another to form networks, the outlines of whose meshes vary according to the tissue in which they occur. In such tissues as muscle and nerve they form elongated meshes whose long axes are parallel to those of the muscle or nerve fibers. In the looser, more areolar tissues they form large meshes of irregular shape. In the capillary mem-

Fig 217 —Diagram of Capillary Bed, Showing Relationship of Arteriole-venular Bridge (Muscular Capillaries) to True (Nonmuscular) Endothelial Capillaries

Typical smooth muscle cells are shown as solid cross lines, branched muscle elements by dotted cross lines. (Zweifach)

branes, as in the walls of the pulmonary alveoli, they are disposed in a close net, the diameter of whose meshes scarcely exceeds that of the capillaries.

With but few exceptions capillaries occur in all the tissues of the body. In epithelium and in cartilage there are no blood vessels of any kind, and in the splenic pulp it is doubtful if true capillaries occur. In certain tissues large vascular spaces occur, which are comparable to the capillaries in that their wall
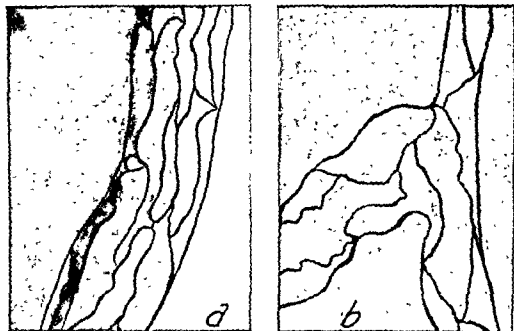
FIG. 218—ENDOTHELIAL CELLS, OUTLINED WITH SILVER NITRATE.

a, in arteriole-venular bridge; *b*, true nonmuscular capillary, from mesentery of frog. (Zweifach)

consists of scarcely more than the endothelial tube, but which differ from the true capillaries in the extreme size of their lumen. These vessels have been described by Minot [6] as *sinusoids* They are found in the erectile tissues, suprarenals, coccygeal gland, parathyroids, pars distalis of the hypophysis cerebri, bone marrow, in the maternal placenta, and in the fetal liver, heart, pronephros, and mesonephros. They differ from capillaries also in that they generally do not connect arteries and veins, but are either exclusively arterial or venous. In the adult only venous sinusoids occur. *Retia mirabilia* are capillary plexuses on arterioles or venules. The best example of a rete mirabile in the human body is the arterial capillary plexus of the glomeruli of the kidney. The intralobular vascular plexus of the liver may be regarded as a venous rete mirabile.
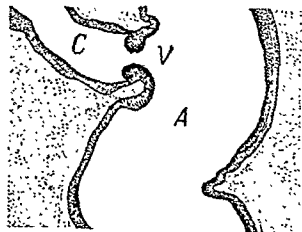
FIG. 219—ARTERIOLE AND CAPILLARY BRANCH SHOWING ENDOTHELIAL VALVE (v) AT CAPILLARY JUNCTION.

(Redrawn from Zweifach.)

Observations of living blood vessels in the mesentery, tongue, skin, and intestinal wall of the frog and in the mesentery and ear of the white mouse have disclosed important details with respect to structure and function, especially of

[6] Minot, 1900.

amphibian larvae has a definite tonicity and is capable of contraction and expansion entirely independent of the presence of any form of periendothelial cell.

The capillaries branch and anastomose with one another to form networks, the outlines of whose meshes vary according to the tissue in which they occur. In such tissues as muscle and nerve they form elongated meshes whose long axes are parallel to those of the muscle or nerve fibers. In the looser, more areolar tissues they form large meshes of irregular shape. In the capillary membranes, as in the walls of the pulmonary alveoli, they are disposed in a close net, the diameter of whose meshes scarcely exceeds that of the capillaries.

FIG 217.—DIAGRAM OF CAPILLARY BED, SHOWING RELATIONSHIP OF ARTERIOLE-VENULAR BRIDGE (MUSCULAR CAPILLARIES) TO TRUE (NONMUSCULAR) ENDOTHELIAL CAPILLARIES.

Typical smooth muscle cells are shown as solid cross lines, branched muscle elements by dotted cross lines. (Zweifach.)

branches, as in the walls of the pulmonary alveoli, they are disposed in a close net, the diameter of whose meshes scarcely exceeds that of the capillaries.

With but few exceptions capillaries occur in all the tissues of the body. In epithelium and in cartilage there are no blood vessels of any kind, and in the splenic pulp it is doubtful if true capillaries occur. In certain tissues large vascular spaces occur, which are comparable to the capillaries in that their wall

collagenous fibers, the greater part of which are circularly disposed. Very few elastic fibers occur even in vessels of this size.

Small Veins.—In the small veins the three coats are fairly distinct, the vascular wall being, however, much thinner than in the artery of corresponding size.

The endothelium of the tunica intima is supported by a very delicate connective tissue membrane which as yet contains but few elastic fibers.

The tunica media consists of a thin layer of circularly arranged smooth muscle cells intermingled with a delicate fibrous tissue; elastic fibers are relatively scarce. The adventitia, though considerably the thickest of the three coats, is as yet a thin membrane. It consists of fibrous connective tissue, elastic fibers being scarcely demonstrable except by means of the specific stains for this tissue.
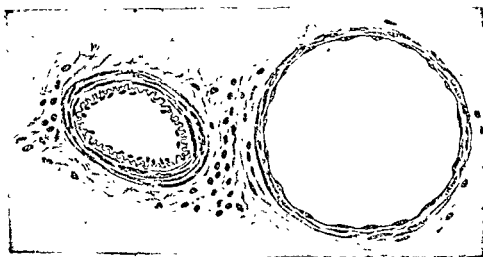
FIG. 221.—TRANSECTION OF AN ARTERIOLE AND VENULE.
×250. (Schafer.)

Larger Veins.—The wall of the larger veins closely resembles that of the corresponding artery, except that the venous wall is much thinner and contains far less elastic tissue. The tunica intima of the medium and large veins presents a lining endothelium, a thin layer of delicate connective tissue fibers, and an incomplete internal elastic membrane. The last named is never so prominent as in the artery.

The tunica media contains smooth muscle cells, the most of which are circularly arranged. A somewhat smaller proportion of delicate connective tissue completes this coat.

The media is best developed in veins of the lower extremities; it forms a thinner layer in veins of the upper extremities, and is relatively scant in the large veins of the abdominal cavity.

The adventitia of the larger veins consists of densely interlacing bundles of collagenous fibers, among which is a network of fine elastic fibers. Occasional small bundles of longitudinal smooth muscle cells occur in the adventitia of the

capillaries.[7] Not all capillaries are functionally active at the same time or to the same degree. Certain capillaries are active even in a resting area. Such an active capillary constitutes a main channel, an arteriolo-venular or a-v bridge between a precapillary artery and a precapillary vein of a unit capillary area (Fig. 217). These a-v bridges are muscular capillaries in contradistinction to endothelial or true capillaries and have a diameter of from 12 to 16 microns (Fig. 218). The true capillaries are abrupt side branches from larger vessels and anastomose freely among themselves. In striated muscle a-v capillaries are relatively infrequent, true capillaries comprising from 75 to 90 per cent of the vessels; in the skin the a-v type of capillary preponderates. A valve-like fold of endothelium occurs at the point of capillary exit in those regions where the capillary offshoot leaves an arteriole or an a-v bridge in a sharp backward angle (Fig. 219) and provides an "endothelial sphincter" which functions to cut off true capillaries from the circulation. Zweifach observed no contractile perivascular elements in true capillaries. Such capillaries, however, possess tone and behave as reversibly distensible tubes.

VEINS

The blood having passed the capillaries, enters the smallest radicles of the venous system, the precapillary venules, and passes thence through the venules to the larger veins. The progressive increase in the caliber of these successive vessels is accompanied by a corresponding increase in the thickness of their wall. Thus, while the endothelial tube alone composes the capillary wall, the endothelium of the precapillary venule is encircled by a delicate connective tissue membrane. In the venule occasional smooth muscle cells are added to the wall of the smaller vessel, and in the vessels of this caliber the fibrous tissues have been so increased that the vascular wall, as in the artery, can be said to possess three coats.
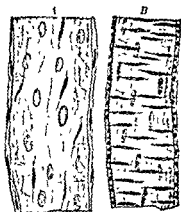
FIG. 220 — PRECAPILLARY VENULE AND ARTERIOLE

The lighter nuclei are those of the endothelium. The darker nuclei in the venule are in connective tissue cells; in the arteriole they are in the muscle cells *A*, venule, *B*, arteriole. Partly diagrammatic Highly magnified

Precapillary Venules.—The wall of the precapillary venule consists of the endothelial lining, which is surrounded by a very delicate connective tissue membrane in which are very few elastic and collagenous fibers.

Venules.—In the venule the tunica intima consists of little more than the endothelial lining. Its media and adventitia are not as yet distinctly differentiated, the former being distinguished only by the incomplete layer of circularly disposed smooth muscle cells. The extremely thin adventitia is composed almost wholly of

[7] Zweifach, 1939.

nate and subclavian, contains collagenous and considerable elastic tissue, the latter often forming incomplete membranous layers, which alternate with the smooth muscle, as in the arteries. Such structure is, however, limited to the very largest of the veins. In the superior vena cava and the hepatic vein the media is practically replaced by adventitia.

The *cranial veins* (cerebral and meningeal) are conspicuous for the almost entire absence of muscle from their walls, the large meningeal sinuses being surrounded by a dense fibrous coat derived from the dura mater, and lined by the usual endothelium. In the veins of the retina also, and those of bones, a media is essentially lacking.

The veins of the *pampiniform plexus* of the spermatic cord are characterized by thick fibromuscular walls, resembling the wall of arteries, but containing only a meager amount of elastic tissue and lacking a clear demarcation between media and adventitia.

The *venous spaces* of the erectile tissues have already been mentioned as presenting to some extent the sinusoidal type of structure, these large venous cavities possessing an extremely thin wall, in structure scarcely more than endothelial lining. The afferent artery projects into the broad vascular lumen, from which the efferent vein makes its exit.

Comparison of the Larger and the Smaller Veins.—Comparing the larger with the smaller veins, the excess of elastic and muscular tissue in the former is most noticeable. In the absence of specific stains, elastic tissue can scarcely be recognized in the venules and smaller veins. In the medium-sized vessels it is scanty, but is present in considerable quantity in the largest vessels.

The precapillary veins and venules contain scarcely any smooth muscle. This tissue becomes more distinct in the small veins and steadily increases proportionately to the size of the vessel; in the largest veins it is again relatively deficient.

Comparison of the Vein with the Artery of Corresponding Size.—The lumen of any given artery is always much smaller than the total lumen of its venae comitantes (usually two in the case of the smaller arteries, one *vena comitans* in the case of the medium-sized), the ratio being about one to three. Hence, of any two vessels in close proximity to each other, the vein would more likely possess the larger caliber; the artery, on the other hand, would have the thicker wall.

As compared with the arteries, the veins are notably deficient in elastic and muscular tissue. In the wall of most veins the white fibrous is in excess of all other tissues. For this reason the adventitia is almost invariably the thickest of the three coats of the vein, whereas in the artery the media is always the thickest coat.

The internal elastic membrane, which can be readily recognized even in the smaller arteries, is limited to the large veins. Alternating layers of elastic and muscular tissues are to be seen even in the medium-sized arteries, but this arrangement is likewise confined to the largest of the veins. The wall of the vein as a whole is much thinner in proportion to its lumen than that of the corresponding artery; it is also less rigid. For this reason the wall of the vein is

largest veins. In these vessels also, a very incomplete external elastic membrane may be demonstrated by the specific stains for elastic tissue.

Nerve fibers and minute blood vessels, vasa vasorum, occur in this coat and distribute their terminal branches to the two outer coats of the vessel. The intima of the vein, as in the artery, is nonvascular. The venae vasorum of veins empty directly into the lumen.
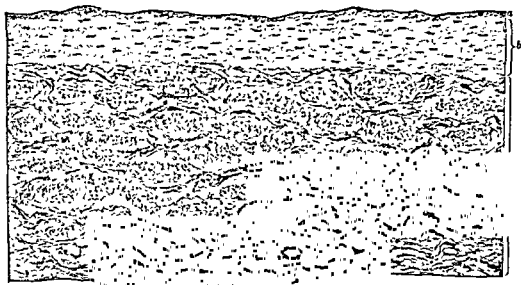
FIG. 222.—TRANSECTION OF THE WALL OF THE HUMAN INFERIOR VENA CAVA.

a, tunica intima; *b*, tunica media; *c*, tunica adventitia. The inner portion of the tunica adventitia contains numerous bundles of longitudinal smooth muscle fibers which have been cut across ×90.

Atypical Veins.—In certain tissues the veins present noticeable departures from the typical structure. *Longitudinal muscle fibers* are found in many of the larger veins of the abdominal and thoracic cavities.

The cephalic, basilic, mesenteric, common iliac, femoral, saphenous, uterine and the dorsalis penis veins contain small longitudinal muscle bundles in the intima Certain veins, *e.g*, saphenous, femoral, and popliteal, contain a layer of longitudinal muscle in the intimal portion of the media.

The suprarenal veins contain, almost exclusively, longitudinal muscle fibers, and in the renal, suprarenal, portal, splenic and phrenic veins and the *inferior vena cava* these fibers form the greater portion of the tunica adventitia.

In the *pulmonary veins* the circular muscle fibers are highly developed, the tunica media of these veins almost equaling in thickness that of the corresponding pulmonary artery. As in other large veins, however, elastic tissue is notably deficient in the tunica media of the pulmonary veins. The muscle of the roots is partially of the cardiac type.

The tunica media of the largest veins, *e g.*, the venae cavae, jugular, innomi-

in the shape of tubes and solid nucleated sprouts (angioblast cords, Bremer) and, converging to form two large vessels, invades the tissue of the embryo in the region of the developing heart as the *vitelline veins*. Subsequently other vessels, both arteries and veins, appear in the embryo. Such vessels are preceded by capillary plexuses, as demonstrated by Evans,[9] in which the definitive vessels arise as paths in the original network selected, enlarged, and modified under the influence of mechanical factors incident to the flow of the main stream of the blood. There can be no doubt that the original primordia of the blood vessels arise by a confluence of separate spaces (angiocysts) —possibly always connected by angioblast cords—and tubes formed in the angioblast; likewise there is no doubt that the embryonic blood vessels sprout as tubes and solid cords and thus grow into adjacent regions (Fig. 216). But the features of vasculogenesis concerning which there remain decided differences of opinion are (1) the nature and origin of the angioblast, that is whether of mesodermal, entodermal or of dual origin; (2) the manner of origin of the primary vascular stems in the embryo, whether by invasion through growth from the extra-embryonic primitive vascular area, or by a process in the body mesenchyma similar to that through which the primitive

FIG 223.—A 13 MILLIMETER HUMAN EMBRYO.

The chorionic vesicle is cut open, revealing the embryo enveloped in the amnion, and the yolk sac (*y.s*). ×1½.

vessels arose in the yolk sac (umbilical vesicle). The evidence seems to favor the mesodermal origin of the angioblast. The advocates of vasculogenesis by invasion (Evans, Minot, Bremer and others) regard the original angioblast, very early differentiated from mesenchyma, as the sole future source of endothelium, to which is ascribed a strict specificity throughout development. The advocates of the *in situ* method of origin (Maximow, Schulte, Miller and McWhorter, Reagan and Thorington and others), on the contrary, conceive early vasculogenesis as a process of progressive fusion of tissue spaces and mesenchymal cells involving a continued differentiation of endothelium from mesenchyma.

The total evidence seems to favor the view that in earliest stages blood vessels may arise in the mesenchyma of the embryo and that these primitive stems may be added by discrete primordia all of which may fuse to form the vascular net out of which develop the future main vessels.

The vessels of later embryonic and fetal stages probably arise solely as sprouts from these earlier stems.

The chief point of uncertainty concerns the point in time when vasculogenesis passes from a process including sprouting and fusion of separate primordia, to one

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[9] Evans, 1909.

much more likely to collapse after death than is the thicker and more rigid arterial wall. Because of the preponderance of muscle in the wall of the artery its contraction in rigor mortis is more powerful than that of the vein; the vein therefore is apt to be distended with blood *while the artery contains but little.* A certain number of blood cells can usually be found in almost any type of blood vessel.

Valves occur at intervals of considerable length along the course of the larger veins. These are not found in the arteries. Each valve consists of one, usually two, and occasionally more crescentic folds or reduplications of the tunica intima between which is a slightly increased amount of connective tissue, the elastic fibers of which are more abundant on the side next the lumen. The valves therefore are suspended free in the lumen of the vessel and are covered on either side with a layer of endothelium which is continuous with that lining the vein.

The valves open with and close against the blood current. They occur generally distal to the point of entrance of venous tributaries. They are more abundant in the veins of the extremities and are lacking in the superior and inferior venae cavae, in the hepatic, portal, renal, uterine, pulmonary, umbilical, cerebral and meningeal veins, in the veins of bones, and generally in veins of less than 2 millimeters diameter. They obviously assist the flow of blood to the heart against the influence of gravity and prevent the reflux of blood. According to Krogh ('22) all veins of striped muscle, down to the smallest branches, are provided with valves. The general absence of valves in the veins of the abdomen and thorax, and their abundance in the veins of the extremities, especially the lower, is probably to be interpreted in terms of a quadrupedal ancestral condition.

Edwards [8] states that the veins at the site of a valve have an elliptical shape in transverse section, *the major axis of the ellipse being parallel with the skin.* The two cusps of the valve arise from the long curves of the ellipse, and the aperture between the free margins of the cusps is also parallel to the overlying skin.

The fact should be borne in mind that it is because of their relative infrequency that valves are not often met with in those transections of the smaller veins which are seen in nearly all microscopical preparations.

DEVELOPMENT OF BLOOD VESSELS

The earliest primordium of the blood vascular system is a *mesenchyma-like* layer, the *angioblast,* which appears between the entoderm and mesoderm at the distal pole of the yolk sac (Fig. 223) at a very early stage of the embryonic development (1 millimeter, Minot). In this layer appear accumulations of rounded cells in the form of anastomosing irregular solid cords. The peripheral cells become flattened to form an endothelial tube; the central cells separate and scatter in the vessels as primordial blood cells floating in a plasma, probably a secretion product of the cells. This network of primitive blood vessels grows toward the embryo

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8 Edwards, 1936.

in the shape of tubes and solid nucleated sprouts (angioblast cords, Bremer) and, converging to form two large vessels, invades the tissue of the embryo in the region of the developing heart as the *vitelline veins*. Subsequently other vessels, both arteries and veins, appear in the embryo. Such vessels are preceded by capillary plexuses, as demonstrated by Evans,[9] in which the definitive vessels arise as paths in the original network selected, enlarged, and modified under the influence of mechanical factors incident to the flow of the main stream of the blood. There can be no doubt that the original primordia of the blood vessels arise by a confluence of separate spaces (angiocysts) —possibly always connected by angioblast cords—and tubes formed in the angioblast; likewise there is no doubt that the embryonic blood vessels sprout as tubes and solid cords and thus grow into adjacent regions (Fig. 216). But the features of vasculogenesis concerning which there remain decided differences of opinion are (1) the nature and origin of the angioblast, that is whether of mesodermal, entodermal or of dual origin; (2) the manner of origin of the primary vascular stems in the embryo, whether by invasion through growth from the extra-embryonic primitive vascular area, or by a process in the body mesenchyma similar to that through which the primitive vessels arose in the yolk sac (umbilical vesicle). The evidence seems to favor the mesodermal origin of the angioblast. The advocates of vasculogenesis by invasion (Evans, Minot, Bremer and others) regard the original angioblast, very early differentiated from mesenchyma, as the sole future source of endothelium, to which is ascribed a strict specificity throughout development. The advocates of the *in situ* method of origin (Maximow, Schulte, Miller and McWhorter, Reagan and Thorington and others), on the contrary, conceive early vasculogenesis as a process of progressive fusion of tissue spaces and mesenchymal cells involving a continued differentiation of endothelium from mesenchyma.

FIG. 223.—A 13 MILLIMETER HUMAN EMBRYO.

The chorionic vesicle is cut open, revealing the embryo enveloped in the amnion, and the yolk sac (*y.s.*). ×1½

The total evidence seems to favor the view that in earliest stages blood vessels may arise in the mesenchyma of the embryo and that these primitive stems may be added to by discrete primordia all of which may fuse to form the vascular net out of which develop the future main vessels.

The vessels of later embryonic and fetal stages probably arise solely as sprouts from these earlier stems

The chief point of uncertainty concerns the point in time when vasculogenesis passes from a process including sprouting and fusion of separate primordia, to one

[9] Evans, 1909.

	Media (elastic tissue)	Media (smooth muscle)	Adventitia
Large artery (typically elastic)	Comprises about one-half of the entire wall	Small relative amount—comprises about one-third of wall	Relatively very thin
Small artery (typically muscular)	Much diminished	Large relative amount—comprises about three-fourths of wall	Somewhat thicker (ratio remains constant for smaller vessels)
Large vein	Small amount	Large relative amount	Large amount
Small vein	Scanty	Small amount	Large relative amount

		LUMEN	WALL	MEDIA (ELASTIC TISSUE AND SMOOTH MUSCLE)	THICKEST LAYER	INTERNAL ELASTIC MEMBRANE	ALTERNATING LAYERS OF ELASTIC AND MUSCULAR TISSUE	VALVES
Medium-sized	Artery	Smaller {Ratio 1 to 3}	Thicker, more rigid	Large amount	Media	Very conspicuous, discernible even in smaller arteries	In small arteries	Absent
	Vein	Larger	Thinner, less rigid	Deficient (collagenous fibers in excess of all other tissue)	Adventitia	Present only in larger veins	In largest veins	Present in some veins

where extension is exclusively by terminal growth. Both arteries and veins have a like origin in capillary plexuses.

The final anastomosing sprouts of endothelium represent the definitive capillaries. The development of the definitive wall of arteries and veins involves the formation of extra-endothelial layers of muscular and connective tissue elements from the surrounding mesenchyma, and their association into the several tunics of the various subdivisions of these vessels.

The essential matters in the foregoing chapter have been summarized in the table on page 186.

HEART

The wall of the heart consists of interlacing bundles of cardiac muscle fibers, the *myocardium*, which are covered externally by the *epicardium*, a serous membrane which forms the visceral layer of the pericardium. Internally the muscular wall of the heart is lined by the *endo-cardium*, which resembles the serous membranes in that it consists of pavement epithelium supported upon a layer of fibro-elastic connective tissue. The endocardium lines all the cavities of the heart, and its endothelium is directly continuous with that of those arteries and veins which are connected with the cavity of the heart. Thus the entire vascular system—heart, arteries, capillaries, lymphatics, and veins—may be said to be lined by an uninterrupted sheet of pavement epithelial cells, the *endothelium*.

FIG 224—VASOFORMATIVE CELLS FROM THE MESENTERY OF A RABBIT SEVEN DAYS OLD

g s, red blood cells; *n*, nucleus of the vascular endothelium; *p*, points of growth, at which extension occurs Highly magnified. (Ranvier.)

Myocardium.—The muscle fibers of the myocardium are so disposed as to form long bundles which by their figure-of-8 arrangement are interwoven with one another to form a dense interlacing mass of muscle bundles. The bundles of the ventricular myocardium begin in tendons inserted into the atrioventricular ring of one ventricle and end in papillary muscles of the opposite ventricle. Because of the irregularity of their disposition, transactions of the cardiac wall present sections of muscle fibers cut in every conceivable direction.

Between the muscle fibers is a very delicate framework of fibrous connective tissue, the *endomysium*, which surrounds the muscle fibers and supports the abundant capillaries, arterioles, and venules, with which they are supplied. The proportion of connective tissue in the normal myocardium as compared with the muscle is, nevertheless, very small.

	Media (elastic tissue)	Media (smooth muscle)	Adventitia
Large artery (typically elastic)	Comprises about one-half of the entire wall	Small relative amount—comprises about one-third of wall	Relatively very thin
Small artery (typically muscular)	Much diminished	Large relative amount—comprises about three-fourths of wall	Somewhat thicker (ratio remains constant for smaller vessels)
Large vein	Small amount	Large relative amount	Large relative amount
Small vein	Scanty	Small amount	Large relative amount

Medium-sized	LUMEN	WALL	MEDIA (ELASTIC TISSUE AND SMOOTH MUSCLE)	THICKEST LAYER	INTERNAL ELASTIC MEMBRANE	ALTERNATING LAYERS OF ELASTIC AND MUSCULAR TISSUE	VALVES
Artery	Smaller { Ratio 1 to 3 }	Thicker, more rigid	Large amount	Media	Very conspicuous, discernible even in smaller arteries	In small arteries	Absent
Vein	Larger	Thinner, less rigid	Deficient (collagenous fibers in excess of all other tissue)	Adventitia	Present only in larger veins	In largest veins	Present in some veins

of endothelial origin (Mall). In this membrane is a network of elastic fibers, and a small amount of smooth muscle. The endothelium of this membrane is continuous with that of those blood vessels which open from the cavities of the heart. Its connective tissue also forms a continuous layer with that of the tunica intima of these vessels; in fact, the three coats of the cardiac wall—endocardium, myocardium, and epicardium—might well be compared with the corresponding three coats of the arterial and venous walls—the intima, media, and adventitia. In either organ, the inner coat consists of a lining membrane of endothelium, and a supporting membrane of connective tissue; muscle in large part composes the middle coat, while the outer coat is typically a connective tissue layer.

Valves.—At the cardiac orifices the entire thickness of the endocardium is folded upon itself to form a double layer, between the folds of which an intervening stratum of dense fibro-elastic tissue is inserted. These endocardial folds form the cardiac valves The number and shape of their cusps are dependent upon the location. The semilunar valves of the aortic and pulmonary orifices consist of three crescentic endocardial folds; at the atrioventricular orifices the tricuspid valve consists of three, the bicuspid or mitral of two, folds.

The margin of the valvular cusp or fold is extremely thin; just within the margin, however, the central mass of dense fibrous tissue is somewhat thickened to form, in each cusp, a dense rim which during valvular closure secures the firm and accurate approximation of the free margins of adjacent cusps. At the apex of the valvular cusp, where the adjacent fibrous margins of the valve meet, the dense connective tissue, particularly in the semilunar valves, is considerably thickened to form a nodule, the *corpus arantii*. These corpora or noduli, in the aged, are frequently subject to calcareous infiltration.

Muscular fibers are continued from the adjacent cardiac wall into the dense fibrous tissue at the base of the valve, except in the case of the semilunar valves of the pulmonary and systemic aortae. This muscle is generally nonstriped, and probably functions as a sphincter. The base of the valve is also surrounded by a ring of fibrous tissue, the *annulus fibrosus*, whose interlacing bundles are so closely packed as to give them an almost cartilaginous feel. At the atrioventricular orifices, these fibrous rings are continuous with the atrioventricular septum, from which the muscle bands of the myocardium take their origin.

Chordae Tendineae.—These are firm, unyielding cords, composed of parallel bundles of dense collagenous fibers, with a few elastic fibers, and covered with a thin endocardium continuous with that of the ventricular wall and cardiac valve. These fibrous bands unite the apices of the papillary muscles to the ventricular surfaces of the mitral and tricuspid valves. At the apex of the papillary muscle the fibrous bundles of the chordae intermingle with the muscle fibers, and are continued into the endomysial connective tissue, which is especially abundant in those portions of the myocardium. At their valvular attachment the fibrous bundles of the chordae tendineae turn almost at right angles, and spread out, in a somewhat radial manner, to become continuous with the dense fibrous tissue which forms the interior of the valve.

In certain portions of the myocardium connective tissue is more abundant. Thus it is slightly increased in the vicinity of the endocardium, in the papillary muscles, and near the bases of the cardiac valves. At the surface of the heart, beneath the epicardium, especially in the various grooves on the surface of the heart, the connective tissue is still more abundant, and may contain groups of fat cells. It is through these accumulations of connective tissue that the larger blood vessels are distributed to the myocardium.
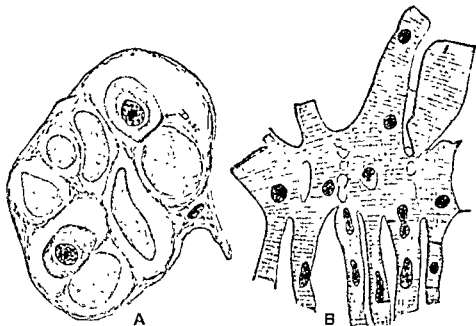
FIG 225.—SECTIONS OF ATRIOVENTRICULAR BUNDLE, FROM THE HEART OF THE BEEF.

A, transverse section of smaller subdivision of the left limb, showing the pericellular lymphoid spaces and the connective tissue capsular stroma. *B*, transition area between atrioventricular bundle and myocardium of the moderator band. The upper portion of this illustration shows Purkinje fibers, the lower portion shows myocardium with band disks. ×1000.

Epicardium.—The epicardium represents the visceral layer of the pericardium and like the other serous membranes, consists of a layer of pavement cells, so joined edge to edge as to form a complete mesothelial coat. Here and there the mesothelium presents small openings at the angles between its cells; these stomata are surrounded by minute, finely granular cells and are perhaps connected with the lymphatic vessels.

The mesothelium of the epicardium is supported upon a thin layer of dense areolar tissue in which are many small blood vessels and lymphatics. Fibers from the deeper surface of this layer are prolonged into the myocardium to become continuous with its endomysial connective tissue. The larger of these connective tissue trabeculae accompany the branches of the larger arteries and veins which are distributed to the muscular wall of the heart.

Endocardium.—The endocardium consists of a lining membrane of polygonal endothelial cells supported upon a thin layer of delicate fibrous connective tissue,

in every species of mammal investigated. It consists of a dense meshwork of cardiac muscle fibers rich in sarcoplasm. It has the form of a band taking origin in scattered fibrils in the posterior wall of the right atrium near the septum in the atrioventricular groove (sinus region; hence, sinoventricular conducting system, Retzer, 1908). It courses forward in the interatrial septum into the upper anterior portion of the interventricular septum, where it divides into two limbs which branch profusely and spread out in a complicated system of terminal branches, the subendocardial Purkinje fibers. Macroscopically the bundle has a grayish appearance. Where it passes from the interatrial to the interventricular

FIG 227.—RECONSTRUCTION OF THE SINOVENTRICULAR SYSTEM (BUNDLE OF HIS) OF THE CALF'S HEART.

(De Witt.)

septum (pars membranacea septi) it expands into the so-called node. In man the right limb is much smaller than the left. The node has a length of approximately 6 millimeters and a diameter of 2 millimeters.

The bundle of the calf's heart has been reconstructed by De Witt.[10] Curran [11] has described a constant bursa or lubricating mechanism in relation with the bundle, furnishing protection against friction during contraction of the heart. He describes "its connection with all parts of both auricles through three large trunks and a number of smaller twigs, and not, as was once thought, merely arising in the right auricle only."

Tawara[12] first carefully described the histology of this bundle in several mam-

[10] De Witt, 1909.
[11] Curran, 1909
[12] Tawara, 1906.

Columnae Carneae.—The columnae carneae are columelliform projections of the myocardium into the ventricular cavity. They consist of cardiac muscle fibers, largely of the Purkinje fiber variety, which are disposed in their long axis, and are covered by reflections and reduplications of the endocardium. The irregular contour of the ventricular cavities appears to be entirely due to the projecting columnae carneae.

These muscular columns may present any one of three modes of attachment to the myocardium: (1) they may be attached along their entire extent; (2) they may be attached only at their two ends, the midportion being free; (3) they may be attached to the myocardium at one end only, the other end projecting into the
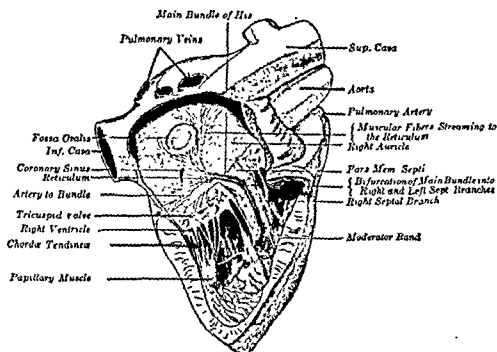
FIG 226—HUMAN HEART OPENED FROM THE RIGHT TO SHOW THE ATRIOVENTRICULAR BUNDLE OF HIS.

The illustration shows also a heart valve, the chordae tendineae, and the papillary muscles (Curran)

ventricular cavity as a *papillary muscle,* from whose apex chordae tendineae pass to the auriculoventricular valves. Either of the last two forms may, in transections of the ventricles, appear as isolated islands of muscular tissue surounded by endocardium and lying apparently free within the cavity of the ventricle. Columnae carneae which span the ventricular cavity constitute *moderator bands.* One such band is frequently present in the right ventricle near the apex, and occasionally one appears in the left ventricle.

Atrioventricular Bundle.—The atrioventricular bundle of His was discovered in the human heart by His, Jr, in 1893 Previously in the same year it had been noted by Kent in the heart of a number of mammals. It has since been seen

the larger veins being always found in the broader connective tissue septa. In the right atrium certain small veins, the *venae minimae* (thebesian veins), empty directly into the cavity of the heart.

The lymph supply is very abundant and intimate. The lymph vessels form two superficial plexuses, the endocardial and the epicardial, both draining into the larger lymph vessels at the base of the heart.

Nerve Supply.—The nerve supply of the vascular system is by means of fine branches from the cerebrospinal and sympathetic systems. *In the heart* these minute nerve trunks end in the various cardiac ganglia, most of which are found in the connective tissue of the heart, *e.g.*, the coronal plexuses about the orifices of the aorta and pulmonary artery. From these ganglia sensory nerve fibers are distributed to the endocardium and epicardium, and motor fibers to the myocardium. The most of the former are connected with the vagus, the latter with the sympathetic trunks. Through both the vagus and the sympathetic trunks are distributed also efferent cerebrospinal fibers: the accessory nerve contributes "inhibitory" fibers through the vagus, the cervical spinal nerves through the inferior cervical ganglia contribute "acceleratory" fibers.

From the cardiac ganglia branches pass to form a coarse plexus in the connective tissue between the muscle bundles, the perimysial plexus, from the branches of which a fine plexus is distributed to the endomysium. The terminal branches end in relation with the surface of the muscle fibers.

The immediate stimuli of heart action are now identified as hormones or "neurohumors," liberated at the nerve terminals. Two such neuronal hormones are recognized and designated as sympathin and acetylcholine; they have antagonistic effects. It is now generally believed that the vagus impulses produce their effect on the heart, a slowing and weakening of the beat, by liberating acetylcholine; and that the sympathetic impulses produce their effect, an acceleration and intensification of the beat, by the liberation of sympathin among the fibers of the muscular wall of the heart. Recent investigations strongly indicate that so-called sympathin is identical with adrenaline.[15, 16]

The pericardium contains numerous encapsulated nerve endings (corpuscles of Golgi and Mazzoni). According to Martynoff [17] unencapsulated endings also are present, of three types· coils, dendriform terminal ramifications, and modified dendriform endings. He describes also naked terminal filaments ending on the bases of the mesothelial covering cells.

The *blood vessels* are similarly supplied, minute ganglia occurring here and there in the adventitia or adjacent connective tissue. From these ganglia sensory branches are distributed to the adventitia and intima and motor branches to the tunica media Naked nerve fibrils can be traced to the smallest blood vessels, and even in the capillaries terminal fibrillae are found in relation with the endothelial wall.

[15] Parker, G H, 1935
[16] Cannon and Lissak, 1939
[17] Martynoff, 1914.

mals, including man. De Witt subsequently extended the study in this same field. "In the sheep and calf, where the fibers are most typical and most clearly differentiated from the myocardial fibers, the fibers are much larger than the myocardial fibers, with fewer fibrils and much more sarcoplasm." She describes the bundle as a muscular syncytium. "Connective tissue and especially elastic fibers are much more abundant than in the myocardium." The bundle contains abundant ganglion cells and nerve fibers. It is also very rich in glycogen. In the ox it is distinctly cellular (Fig. 115).

It would seem, on the basis of its constancy of presence and structure, and its probably independent blood and nerve supply, that the atrioventricular bundle has a function independent of the myocardium. This is of the nature of a neuromuscular end-organ (Retzer; De Witt), providing for the conduction of the impulse to contraction, and the coördination of the atrial and ventricular rhythm.

A *muscle bundle of closely similar structure intimately related with the vagus* and sympathetic nerves, the *sino-atrial node*, has been described by Keith and Flack (1907) at the juncture of the sinus venosus and the atrium. It is believed to be the place of origin of the impulse to the heart beat, from which it is transmitted to the atrioventricular bundle.

Laurens [13] has described an analogous muscular connection between auricles and ventricles in certain reptiles, where it assumes the form of an inverted funnelshaped tube.

Development.—The primordium of the heart arises from the fusion of a pair of parallel endothelial tubes in the paramedial angioblast, each surrounded by primitive mesenchyma. The endothelium of the resulting sac differentiates into the endocardium of the definitive heart, while the connective tissue and muscle develop from the mesenchyma in a manner essentially similar to that described for the blood vessels.

Blood Vessels.—The heart is supplied with blood through the two coronary arteries These are branches of the aorta, arising at its base, at the sinuses of Valsalva. The larger branches of the coronary arteries pursue their course beneath the epicardium in the superficial grooves of the cardiac wall. From these large arteries, smaller branches are distributed to the epicardium and to the muscular wall, the latter vessels penetrating as far as the endocardium, in whose connective tissue they form a meager capillary plexus. Minute blood vessels may persist from the fetal condition in some of the valves in a small percentage of hearts, occurring most frequently in the aortic leaflet of the mitral valve.[14] The coronary arteries are peculiar in that the media is divided into two lamina by a fenestrated membrane.

The capillaries of the myocardium are extremely abundant. They form elongated meshes between the muscle fibers, the circumference of each muscle fiber being in relation with several capillary vessels. The veins return the blood from · these rich capillary plexuses and pursue a course similar to that of the arteries,

13 Laurens, 1913
14 Kugel and Gross, 1926.

crons,[3] varying in size from 0.5 to 1.0 micron. The number varies with the fat content of the food and the time following a meal. The chylomicrons are best seen with the dark field microscope. In dry smear preparations they may be confused with the hemoconia ("blood dust"), the fragments of disintegrated effete blood
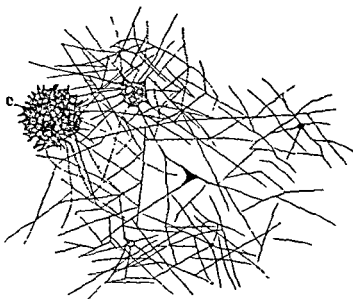
FIG 228—FIBRIN FIBRILS, AND GROUP OF PLATELETS (*c*). (Ellenberger and V. Schumacher.)

cells. After the digested fat has passed through the intestinal mucosa it is carried *via* the lacteals, thoracic duct and right lymphatic duct to the blood stream where it appears as chylomicrons. These are converted in part into lecithin in the liver. Lecithin is absorbed by the membrane of the red blood corpuscles and constitutes a variable component of that structure.

THE RED BLOOD CELL

The cells of the peripheral blood comprise the so-called erythrocytes and the leukocytes. Since the red "cells" in the definitive condition are anucleate, they are more appropriately designated *erythroplastids* or red blood corpuscles. They are biconcave disks, the biconcavity representing a compensatory bipolar collapse of the originally spheric cell following the appearance of a central cavity as a result of the resorption or extrusion of the nucleus. In profile view these corpuscles have the form of a dumbbell. A variable small proportion of the red corpuscles has a saucer or cup shape.[4, 5, 6] This shape signifies a secondary modification, the initial result of the operation of either mechanical or osmotic factors. The discoid cor-

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[3] Gage and Fish, 1924
[4] Weidenreich, 1905
[5] Lewis, F. T, 1904.
[6] Minot, 1900

CHAPTER VIII

BLOOD

The circulating blood and its source of origin, the red bone marrow, constitute an integral organ conveniently designated the "*erythron.*"[1] This organ comprises a parenchyma and an interstitial tissue or stroma, as shown in summary in the following table. In the circulating blood the *plasma* represents the interstitial tissue,

ERYTHRON
        Circulating blood
            Cells (red blood corpuscles)
            Plasma (interstitial tissue)
        Organ of origin (bone marrow)
            Blood cells (parenchyma)
            Interstitial tissue {fat
                                {reticulum

the definitive red blood cells constitute the parenchyma; in the bone marrow the stroma comprises the reticular connective tissue and fat, red blood cells at all stages of development forming the parenchyma. The white blood cells, also produced in part in the bone marrow, are not strictly a component of the erythron. The blood and bone marrow constitute each approximately 5 per cent of the body weight. The cells of the circulating blood occupy from 40 to 50 per cent of the total volume. The total volume of the erythron, exclusive of plasma and fat, is approximately 3500 c.c., which represents an organ considerably larger than the liver.

When blood begins to clot an additional morphologic element appears, namely *fibrin.* These fibrin fibrils enmesh the blood cells and produce a *thrombus.* According to a generally accepted theory of coagulation, both fibrinogen and prothrombase occur in solution in the plasma. Thrombokinase (cephalin) is liberated by the blood platelets. The thrombokinase in the presence of calcium converts the prothrombase into the active enzyme thrombase (*thrombin*), which precipitates fibrin from the fibrinogen. The defibrinated blood plasma constitutes the *serum.* Howell[2] compares the process of clotting to crystal formation, "an aggregation of the invisible particles (amicrons) to visible particles and then the further consolidation of these particles into rigid looking needles." Vitamin K is necessary for the normal production of prothrombase.

Ordinarily the blood plasma contains small spheric lipoid bodies, the *chylomi-*

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[1] Boycott, 1913
[2] Howell, 1914.

The daily blood destruction involves a loss of twenty-five grams of hemoglobin from the circulating blood, which must also be replaced, probably through the medium of the reticuloendothelial system, especially those portions resident in liver, spleen and bone marrow. The total surface area of the red blood corpuscles is approximately 3,000 square meters, about fifteen hundred times the surface of the body.

The red elements of all mammals are non-nucleated. The lower forms have nucleated elements (erythrocytes), frequently of ellipsoidal form. Mammalian red elements of greatly divergent sizes (2.5 μ in musk ox; 9.4 μ in elephant; dog, 7.5 μ) are all of circular outline, except those of the camelidae (llama, camel, etc.) which are elliptical. The erythroplastids are generally believed to be inclosed by a delicate membrane, and to contain a very delicate stroma (spongioplasm) and fluid matrix (hyaloplasm, with hemoglobin). The red corpuscles have a tendency when exposed, as in a drop mounted under a cover slip, to arrange themselves in rows, like coins in a pile, concave surfaces apposed, forming *rouleaux*. Drop preparations show after a short time also an increasing number of plastids with puckered or spiny surfaces, *crenated* corpuscles. This condition results from evaporation producing a medium of greater density than that of the normal blood plasma. Any medium of density equal to that of the plasma of any particular blood is spoken of as an *isotonic* solution for that blood. The solution in most common use for human blood is a 0 9 per cent solution of sodium chloride in distilled water. Solutions of higher density are *hypertonic*; these produce exosmotic currents causing destruction leading through *crenation*. Solutions of lower density, for example, water, are *hypotonic*; they produce destruction (hemolysis) through endosmosis causing swelling, a stage of which shows a saucer-shaped corpuscle. This is accompanied by laking, or extraction of hemoglobin, giving rise to *blood shadows;* and final bursting, leaving a débris called *hemoconia.*

FIG. 230. — BLOOD CELLS FROM A SPECIMEN OF FRESHLY DRAWN, UN-STAINED HUMAN BLOOD.

A, red blood corpuscles, deep focus, showing a light center and dim margin; *B,* the same with a higher focus; the center, being slightly out of focus, is dim while the margin is light; *C,* crenated red corpuscles from the margin of the preparation; *a,* deep focus; *b,* higher focus; *D,* two polymorphonuclear leukocytes; *E,* large mononuclear leukocyte. × 750.

FIG. 231 — DIAGRAMS SHOWING THE ACTION OF WATER UPON THE RED BLOOD CORPUSCLE.

a, the corpuscle in profile; *b-e,* various stages in the transformation which leaves only a shadow, *e* (Schäfer.)

The number of red corpuscles in the blood is subject to constant variation between wide limits. Many physiologic conditions influence their total number, as well as the relative proportion of red elements to the white. The average number of red corpuscles in the adult male is about 5,000,000 per cubic millimeter. In young robust persons the number may be considerably higher. The

puscles have a diameter in smears of approximately 7.5 microns; suspended in plasma they measure 8 8 microns. They are enveloped by a lipoid membrane and consist essentially of a very limited cytoplasmic stroma supporting the hemoglobin, probably in amorphous condition. The hemoglobin content represents about 35 per cent of the volume. The most efficient mechanism for the transport of oxygen is one where all of the hemoglobin is readily accessible for chemical union. This condition is met perfectly by the biconcave-disk form of the erythroplastid. No
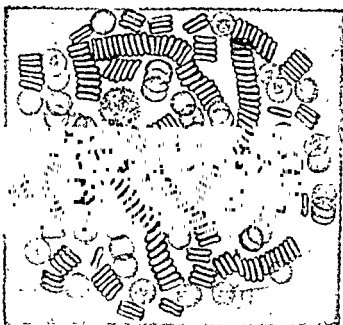
Fig 229.—From a Freshly Prepared, Unstained Specimen of Human Blood.

Three leukocytes, an eosinophil, a polynuclear, and a lymphocyte, are represented. Many red blood corpuscles (erythroplastids), some lying flat, some in rouleaux and in profile, are also shown × 1200, but reduced somewhat in reproduction. (Schäfer.)

part of the disk is more than 0.85 micron from the surface. In a spheric corpuscle of the same volume the center would be at least 2.5 microns from the surface. Moreover, such spheric corpuscles are estimated to have a surface area 20 per cent less than that of the biconcave disk.

With the data of normal blood volume (5 per cent of body weight; 5 to 6 liters) and the number of red blood corpuscles per cubic millimeter of blood (5,000,000), an estimation of the total number of erythroplastids is readily made, namely, twenty-five trillion. It is now generally agreed that the duration of life of the red blood corpuscle is about thirty days.[7, 8, 9] On this basis approximately 750 billion red corpuscles would disintegrate every twenty-four hours, or from seven to ten million every second. These must be replaced from the bone marrow.

[7] Ashby, 1919
[8] Escobar and Baldwin, 1934.
[9] Gordon and Kleinberg, 1938

(c) granulocytes
    neutrophilic
    eosinophilic
    basophilic
    platelets (thromboplastids)
In bone marrow
  megakaryocytes
  plasma cells
  Russell-body cells
  mast cells

Lymphocytes.—The lymphocytes are separable into three varieties: large, intermediate and small. These are genetically related and connected by transitional stages Large lymphocytes divide to produce medium-sized daughter cells, which latter may again divide to produce small lymphocytes. Small lymphocytes grow to
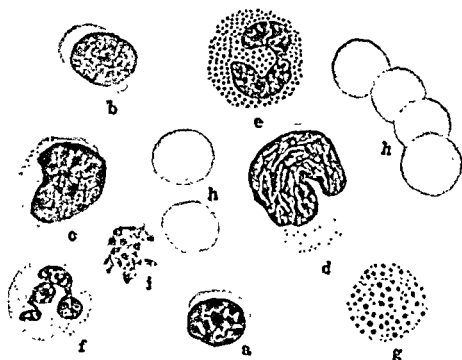
FIG. 235—A GROUP OF CELLS FROM NORMAL HUMAN BLOOD.

a, small lymphocyte; b, medium-sized lymphocyte; c, large lymphocyte (cytoplasm contains azurophilic granules); d, monocyte, e, eosinophil leukocyte; f, neutrophil (polymorphonuclear) leukocyte, g, basophil leukocyte, h, red blood corpuscles, in surface view, i, a group of blood platelets. Wright's stain. × 1200.

intermediate size and may subsequently grow to large size. Lymphocytes of all sizes have common cytologic features: relatively large spheric nucleus and narrow envelop of basophilic cytoplasm. In dry smears stained with Wright's stain the cytoplasm may show a variable small number of azurophilic (metachromatic) granules. The nucleus appears chromatic, with the chromatin for the most part arranged in relatively large angular or rounded blocks, some adherent to the nuclear wall. Lightly stained with Heidenhain's iron hematoxylin a nucleolus becomes discernible in some of these cells. With the usual stains the chromatic nucleolus
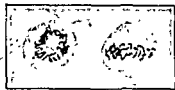
FIG. 232.—TWO RETICU-
LATED RED BLOOD COR-
PUSCLES (RETICULO-
CYTES) SHOWING THE
STAINABLE NETWORK
STAINED SUPRAVITALLY
WITH BRILLIANT CRESYL
BLUE. × 1200.

number may also be much reduced by considerable hemorrhages or by the imbibition of large quantities of fluid. Profuse perspiration tends to produce concentration of the blood and an apparent increase in the number of its corpuscles. The number of red blood corpuscles in the female is slightly less than in the male, about 4,500,000 per cubic millimeter. The average life of an erythroplastid is approximately 30 days. According to Wearn, Warren and Ames [10] it may be close to 100 days. In the guinea-pig the longevity of the erythrocytes is given as from 22 to 28 days.

FIG. 233.   FIG. 234.

FIG. 233.—FIVE NUCLEATED RED CELLS (ERYTHROCYTES) FROM THE BLOOD OF A FROG. Eosin-methylene blue. Hastings' method. ×1200.

FIG. 234.—THREE RED BLOOD CELLS FROM THE MARROW OF A HUMAN RIB. ×1200.

THE WHITE BLOOD CELLS

The leukocytes of the circulating blood comprise the *lymphocytes*, the *monocytes* and the *granulocytes*. In addition, there occur granular plastids, the blood *platelets* or *thromboplastids*. The normally noncirculating leukocytes of the bone marrow include *megakaryocytes, plasma cells, Russell-body cells* and *mast cells.* Under certain pathologic conditions (*e.g.*, myelogenous leukemia) all of the latter group of leukocytes may enter the blood stream in variable numbers. The following table lists the varieties of blood cells. The normal average number of leukocytes per cubic millimeter is 8,000.

Blood cells in
the circulation
{
Red—erythroplastids
            (red blood corpuscles)
White—leukocytes
    (*a*) lymphocytes
            large
            medium
            small
    (*b*) monocytes
            spheronuclear
            reninuclear

10 Wearn, Warren and Ames, 1922.

Granulocytes.—P. Ehrlich in a series of communications announced that by coloring the leukocytes with various stains he was able to distinguish by their reaction, several types of granules. These he called (α) oxyphil or acidophil, which were deeply stained by eosin, acid fuchsin, etc.; (β) amphophil, which were stained both by eosin, and by dahlia and like dyes; (γ) basophil, which were stained deeply by dahlia, thionin, etc.; (δ) certain cells which neither after staining with eosin, etc , nor with dahlia, etc., could be made to show any granules other than the nodes of cytoreticulum; (ε) neutrophil, which can be stained only by a due admixture of acid and basic dyes, such as a mixture of fuchsin and methylene blue, or the so-called "triacid mixture" of Ehrlich.

The demonstration of these characteristics presupposed a division of dyes into three primary classes: (1) acid—e.g., eosin, orange G, acid fuchsin, aurantia, erythrosin, (2) basic—e.g , methylene blue, dahlia, thionin, hematin; (3) neutral—which are only formed by the interreaction of examples of each of the two preceding classes; the neutral dye is supposed to arise de novo in such mixtures, as a result of chemical reaction.

The application of such a classification of stains to other tissues than the blood has, however, been found to present considerable difficulties.

FIG. 237.—OUTLINE DRAWINGS OF LIVING POLYMORPHONUCLEAR LEUKOCYTES OF RABBIT, FROM A DROP OF BLOOD MIXED WITH RINGER'S SOLUTION TO WHICH A SMALL AMOUNT OF HIRUDIN HAD BEEN ADDED TO PREVENT COAGULATION.

In the course of half an hour the cells develop retractile undulatory processes. *a*, hyaline-surface phase; *x*, hyaline layer; *b*, and *c*, ciliated phase; *d*, flagellated phase. Leukocytes of all classes of vertebrates undergo similar changes. (Kite, *J. Infect. Dis.*, 1914, 15:2)

According to Kite the cytoplasm of the polymorphonuclear leukocytes has nothing of the nature of a cell membrane. These cells are described as completely naked, and are said to contain neither spongioplasm nor hyaloplasm. "The cytoplasm is a jelly in which are embedded large numbers of globules." The structures usually termed cytoplasmic granules are of the nature of separation products; they do not grade into the surrounding cytoplasm. All leukocytes undergo also certain definite structural transformations, characterized by the appearance of pseudopods changing into vibratile cilia Kite [11] suggests that the protoplasmic processes may be prominently concerned in phagocytosis. Under certain conditions erythroplastids may be made to protrude similar processes.

Granulocytes comprise three varieties separable on the basis of their differential staining reaction to mixtures of basic and acid dyes, e.g., eosin and methylene blue. as in Wright's stain: *neutrophilic, eosinophilic* and *basophilic*. These cells in definitive condition have a lobulated, polymorphous, "chain" nucleus. The nucleus of the *neutrophils* has from three to five lobules; that of the *eosinophil* has a maximum of three lobules The neutrophils are characterized by minute granules,

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[11] Kite, 1914

cannot be discriminated from the ordinary chromatin blocks. Stained supravitally with Janus green B and neutral red the cytoplasm reveals the presence of a small number of mitochondria and neutral red bodies ("segregation apparatus"). With appropriate staining also a Golgi reticular apparatus and a cytocentrum can be disclosed. From 20 to 35 per cent of the leukocytes of the normal adult are lymphocytes, those of smaller size predominating. Nothing is definitely known regarding the duration of life of the lymphocytes; it is generally considered to be potentially relatively long in comparison with other circulating leukocytes.

As concerns the function of the lymphocytes two contradictory claims are held. One group of hematologists regards the lymphocyte as a definitive, highly specialized cell with important, largely unknown functions. This group ascribes to the lymphocytes among their probable functions some connection with fat metabolism and immunity, antitoxic and healing reactions. The opposing group of hematologists regards the lymphocytes as relatively undifferentiated embryonal cells with multiple developmental capacities. Among these potentialities, possibly in addition to those enumerated above, this group recognizes the capacity to differentiate into monocytes, into granulocytes, and even into erythrocytes. What determines which particular developmental capacity of these polyvalent cells shall gain expression is assumed to be the impingement of a particular differential environmental stimulus. For example, the factor of relatively high CO_2 tension, such as prevails in the sluggishly moving or static blood of the venous sinuses of the red bone marrow, stimulates the elaboration of hemoglobin; bacteria and their toxins stimulate the elaboration of neutrophilic granules; tissue débris stimulates the elaboration of eosinophilic granules and the differentiation of some of the lymphocytes into phagocytic monocytes. The eosinophilic granules presumably contain an enzyme which renders the tissue débris more readily digestible by the monocytes.

FIG. 236—GROUP OF THREE SMALL AND TWO LARGE BLOOD PLATELETS. ×2000.

Monocytes.—The monocytes may be classified as spheronuclear and reninuclear. These terms are self-explanatory. The spheronuclear are the younger forms of monocytes They more closely resemble the parent large lymphocytes. However, the definitive monocytes as a group have certain differential features by which they may be discriminated from the large lymphocytes. The nucleus is relatively smaller, the cytoplasmic envelop relatively wider. With proper staining with iron hematoxylin a nucleolus may sometimes be disclosed, especially in the spheronuclear variety. The chromatin occurs more largely in the form of coarse threads; the nucleus has a stringy appearance. A cytocentrum is frequently conspicuous, located in the nuclear indentation in the reninuclear variety. The cytoplasm may contain also azurophilic granules, sometimes in considerable numbers, and, as compared with lymphocytes, more numerous mitochondria and a more voluminous segregation apparatus and a somewhat larger Golgi net. The monocytes normally constitute about 4 per cent of the leukocyte total; they are notably phagocytic for fluids and larger particles, and function as *macrophages*.

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present in eosinophils. Mitochondria are said to be totally absent in the erythro-plastids of normal adult human blood.[17]

The noncirculating leukocytes of the bone marrow include the megakaryocytes, plasma cells, Russell-body cells and mast cells.

Megakaryocytes.—The *megakaryocytes* are hemogenic giant cells. Similar cells in the yolk sac may produce erythrocytes;[18] in normal bone marrow these cells only produce platelets, segmentation products of pseudopods protruded into the venous sinuses.[19] Under experimental conditions certain megakaryocytes of bone marrow may be stimulated to produce erythrocytes.[20] Platelets may be formed also by mass fragmentation of the perinuclear cytoplasm. The resulting naked nuclei may pass into the circulation and get caught in the capillaries of the lung, where they disintegrate. Temporarily such naked nuclei in the pulmonary capillaries may act as a barrier against which circulating platelets may cohere giving the appearance of original megakaryocytes. This condition may have significance in relation to the recent claim that the lung is a supplementary source of blood platelets.[21] The fetal spleen and liver also contain megakaryocytes.[22]

In the bone marrow, megakaryocytes (myeloplaxes) may be confused with osteoclasts. The nucleus of the megakaryocyte is generally complexly polylobular. In later stages this nucleus may become resolved more or less extensively into separate bodies, producing a multinucleated condition. As such, with the usual technic, it resembles the polynuclear osteoclasts. With Wright's technic only the megakaryocytes show the metachromatic granules characteristic of the platelets. Osteoclasts are essentially foreign body giant cells; they represent fusion products of originally discrete reticular cells and osteoblasts.[23] The polynuclear megakaryocytes represent hypertrophied hemocytoblasts, whose nucleus first became polylobular and ultimately was partitioned by process of amitotic nuclear division.

Plasma Cells.—Plasma cells are normal constituents of bone marrow; they occur generally in groups, more frequently in relation to areas of red cell formation. Their size is generally that of intermediate lymphocytes. Their differential features include deeply basophilic cytoplasm, small chromatic eccentric nucleus, and small oval or crescentic lightly staining juxtanuclear area. The chromatin is generally so arranged as to give a "cart wheel" appearance.

Russell-body Cells.—Russell-body cells are derivatives of plasma cells. They occur only with extreme rarity in normal bone marrow. They are more numerous in the spleen, lymph nodes and hemal nodes. They are characterized by the presence of oxyphilic granules and globules of greatly varying size. These cells may attain a size several times that of the parent lymphocyte and may contain many globules. The globules, or Russell bodies, are also designated *fuchsinophil bodies.*

[17] Cowdry, 1914.
[18] Jordan, 1916
[19] Wright, 1910.
[20] Kleinberg, Gordon and Charipper, 1939.
[21] Howell and Donahue, 1937.
[22] Kingsley, 1935.
[23] Jordan, 1918.

the eosinophils by coarse granules. The neutrophils are the *microphages* of Metchnikoff; they are predominantly phagocytic for pus-forming bacteria; they range in size from 7.5 μ to 10 μ in diameter. The eosinophils have normally only very slight phagocytic capacity. Both contain mitochondria, Golgi apparatus, neutral-red bodies and cytocentrum. Under normal conditions the neutrophils (heterophils) constitute from 55 to 70 per cent of the leukocyte total, the eosinophils about 4 per cent. According to Osgood,[12] the life duration of the neutrophil is from two to three days, that of the eosinophil from eight to twelve days.

The significance of the *basophils* is puzzling. They constitute only 0.5 per cent of the leukocyte total. On the basis of comparative studies of the blood of amphibia, reptiles and birds they are divisible into two varieties: (1) Cells with spheric lymphocyte-like nucleus and coarse orthobasophilic granules of uniform size and spheric shape. These cells have mitochondria, Golgi apparatus, neutral red bodies and cytocentrum. *In the marrow of reptiles and birds these basophils ripen into* eosinophils. Transitional "hybrid" granulocytes with mingled basophilic and eosinophilic granules occur. These basophils are unripe eosinophils. (2) Cells with irregular vesicular "degenerate" nucleus, and irregular angular metachromatic granules of very unequal size. The cells generally defy demonstration of mitochondria, Golgi apparatus and cytocentrum. They have all the earmarks of senile cells and may be interpreted as abortive immature eosinophils. Basophils are said to have a life tenure of from twelve to fifteen days.[13] The granules of the basophils dissolve readily in aqueous solutions. Under certain pathological conditions the basophils increase in number, in general concomitantly with an increase of eosinophils. They apparently have no relation to the basophilic granular mast cells of the tissues.[14]

Platelets.—These commonly hold positions at the center of masses of converging fibrin fibrils in blood clots, in consequence of which they are supposed to be the essential elements in clotting, liberating thrombokinase, hence their synonym *thrombocyte*. This term, however, is ill-chosen, for these elements contain no nucleus. What simulates a nucleus is the central spheroidal mass of basophilic granules. Blood platelets are capable of ameboid motility. They vary in diameter from 2 to 4 microns, and in number per cubic millimeter from 400,000 to 800,000.[15] Wright's observations on mammalian megakaryocytes furnish at present the best data for the genetic interpretation of platelets.[16] However, almost every conceivable mode of origin, notably from extruded nuclei of erythrocytes, and as precipitation artifacts, still claims supporters.

Cowdry has demonstrated mitochondria, by vital staining with Janus green, in all types of leukocytes, except mast leukocytes, including platelets. The lymphocytes and polymorph neutrophils contain them abundantly. They are only sparsely

[12] Osgood, 1937
[13] Osgood, 1937.
[14] Maximow, 1913
[15] Dameshek, 1932.
[16] Wright, 1910.

present in eosinophils. Mitochondria are said to be totally absent in the erythro-plastids of normal adult human blood.[17]

The noncirculating leukocytes of the bone marrow include the megakaryocytes, plasma cells, Russell-body cells and mast cells.

Megakaryocytes.—The *megakaryocytes* are hemogenic giant cells. Similar cells in the yolk sac may produce erythrocytes;[18] in normal bone marrow these cells only produce platelets, segmentation products of pseudopods protruded into the venous sinuses.[19] Under experimental conditions certain megakaryocytes of bone marrow may be stimulated to produce erythrocytes.[20] Platelets may be formed also by mass fragmentation of the perinuclear cytoplasm. The resulting naked nuclei may pass into the circulation and get caught in the capillaries of the lung, where they disintegrate. Temporarily such naked nuclei in the pulmonary capillaries may act as a barrier against which circulating platelets may cohere giving the appearance of original megakaryocytes. This condition may have significance in relation to the recent claim that the lung is a supplementary source of blood platelets.[21] The fetal spleen and liver also contain megakaryocytes.[22]

In the bone marrow, megakaryocytes (myeloplaxes) may be confused with osteoclasts. The nucleus of the megakaryocyte is generally complexly polylobular. In later stages this nucleus may become resolved more or less extensively into separate bodies, producing a multinucleated condition. As such, with the usual technic, it resembles the polynuclear osteoclasts. With Wright's technic only the megakaryocytes show the metachromatic granules characteristic of the platelets. Osteoclasts are essentially foreign body giant cells; they represent fusion products of originally discrete reticular cells and osteoblasts.[23] The polynuclear megakaryocytes represent hypertrophied hemocytoblasts, whose nucleus first became poly-lobular and ultimately was partitioned by process of amitotic nuclear division.

Plasma Cells.—Plasma cells are normal constituents of bone marrow; they occur generally in groups, more frequently in relation to areas of red cell forma-tion. Their size is generally that of intermediate lymphocytes. Their differential features include deeply basophilic cytoplasm, small chromatic eccentric nucleus, and small oval or crescentic lightly staining juxtanuclear area. The chromatin is generally so arranged as to give a "cart wheel" appearance.

Russell-body Cells.—Russell-body cells are derivatives of plasma cells. They occur only with extreme rarity in normal bone marrow. They are more numerous in the spleen, lymph nodes and hemal nodes. They are characterized by the pres-ence of oxyphilic granules and globules of greatly varying size. These cells may attain a size several times that of the parent lymphocyte and may contain many globules. The globules, or Russell bodies, are also designated *fuchsinophil bodies*.

[17] Cowdry, 1914.
[18] Jordan, 1916.
[19] Wright, 1910
[20] Kleinberg, Gordon and Charipper, 1939
[21] Howell and Donahue, 1937.
[22] Kingsley, 1935.
[23] Jordan, 1918.

In the larger cells the nucleus is compressed and distorted and has a peripheral location. The globules may be of crystalloid form and resemble hemoglobin crystals. While clearly not normal definitive hemoglobin, the material of these cells might be regarded as aborted hemoglobin, and the cells as abortive erythroblasts at a later stage than that represented by the plasma cell.

That these cells are not *hemophages* as claimed by Michels [24] becomes clear from a comparative study of Russell-body cells and macrophages with ingested erythroplastid fragments in hemal nodes. Stained with eosin-azure the globules of the macrophages with hemoglobiniferous débris have a golden yellow or light brown color, the globules of the Russell-body cells have a pink or light red color.

Mast Cells.—The mast cells of the marrow are identical with those of the subcutaneous tissue. They resemble closely blood basophils ("mast leukocytes") but they are not true blood cells. Though identity with basophilic blood leukocytes has been claimed for the tissue mast cells, Maximow's [25] conclusion that they are distinct and unrelated cells is now generally accepted. According to Holmgren and Wilander, [26] they produce heparin, a blood anticoagulant.

HEMOGLOBIN

Hemoglobin is a complex chemical compound of the protein globin with an iron-containing body, *hematin;* it gives the characteristic color to the blood. It combines readily with oxygen to form *oxyhemoglobin,* a loose chemical combination by which the oxygen is carried from the lungs to the tissues, and which gives the brighter red color to the arterial as compared with the venous blood. The hemoglobin is held either in solution or in unstable chemical union by the cytoplasm of the erythroplastids. [27] It escapes from these corpuscles after rupture, or it may be extracted by ether, and is then prone to crystallize on evaporation in the form of minute brownish-yellow prisms. The crystals of the various species of any genus belong to a crystallographic group (Reichert) but generic differences are frequently striking; thus, in human blood they are long rhombohedra (Fig. 238), in guinea-pig, tetrahedra, in squirrel, hexagonal plates, in rat, elongated six-sided plates, in hamster (a rodent), rhombohedra, and in dog they appear as rhombic prisms which are diamond shaped in cross-section.

Various other crystalline, and also amorphous hemoglobin derivatives may occur as decomposition products. The iron of the coloring matter of the hemoglobin may be thus obtained in the form of *hematin,* a soluble, amorphous protein compound of a brownish-red color. If hematin is combined with hydrochloric acid the chloride of hematin, *hemin,* is produced. Hemin occurs in deep brownish-red crystals, known also as *Teichmann's crystals,* which differ somewhat *according to* the animal species from which they are obtained; those of human blood take the

24 Michels, 1935.
25 Maximow, 1913
26 Holmgren and Wilander, 1937.
27 Kite, 1914

form of triclinic plates (Fig. 239). Hemin
crystals derive a certain importance as
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and they may be obtained from old and
dried-up specimens as readily as from
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Hematin may decompose also into
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ocytic leukocytes as the product of cellular
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FIG 238.—HEMOGLOBIN CRYSTALS.

a and *b*, from human blood; *c*, from the
cat; *d*, from the guinea-pig; *e*, from the
hamster; *f*, from the squirrel. (Ranvier.)

spleen and bone marrow. Iron in the tissues, and ferruginous pigments gener-
ally, can be recognized by application of the ferrocyanide test, which stains the
iron blue.

FIG. 239.—CRYSTALS OF
CHLORIDE OF HEMATIN OR
HEMIN. (Ranvier.)

When extravasations of blood occur within the
tissues of the body, as, for example, in the corpus
hemorrhagicum of the ovary, the hematin is frequently
deposited as *hematoidin,* an iron-free derivative of hemo-
globin which forms stellate group of yellowish needle-
like crystals. Hematoidin is apparently identical with
bilirubin, a bile pigment.

HEMOPOIESIS

The earliest seat of *blood formation* is in the wall
of the yolk sac. Following the fifth week of embryonic
life blood formation shifts to the reticular stroma and
sinusoids of the liver. From the fourth to the sixth week there is some hemopoietic
activity also in body stalk, the body mesenchyme and the mid-ventral portion of the
aorta. Towards the end of the second month the spleen becomes an active locus

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27 Kite, 1914.

granulocytes, and one for the lymphocytes and monocytes. Polyphyletists make the claim of distinct ancestors for erythrocytes, granulocytes, lymphocytes and monocytes; and in extreme form, of separate ancestors also for each variety of granulocyte.

Probably the most widely accepted theory of hemopoiesis is that of Doan, Cunningham and Sabin ('25) based largely on studies of avian bone marrow. This theory is essentially polyphyletic, since it recognizes distinct ancestors for erythrocytes, clasmatocytes (macrophages), granulocytes, monocytes and lymphocytes However, it is unique in that it derives the erythrocytes from endothelial cells separating from the lining of "intersinusoidal capillaries" of the bone marrow.

POLYPHYLETIC CONCEPT OF BLOOD CELL ORIGIN
(Scheme according to Doan, Cunningham and Sabin)
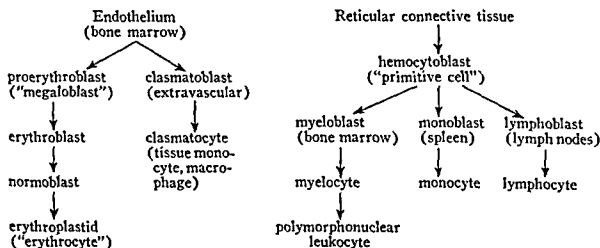
It starts with the concept of a "reticulo-endothelial system" (Aschoff, '24). Reticular connective tissue cells round up and separate from the stroma as "primitive cells." These differentiate along three distinct lines as myeloblasts, monoblasts and lymphoblasts, and eventuate respectively in definitive granulocytes, monocytes and lymphocytes. Cells which separate from the luminal side of the endothelial lining of the capillaries (sinusoids) differentiate progressively to become "megaloblasts," erythroblasts, normoblasts and erythrocytes; those which separate from the stromal side of the capillaries are said to become clasmatocytes. This theory is summarized in the foregoing scheme. Aside from the question of the verity of polyphyletic concepts, this theory is dubious at least in so far as concerns the claim of an endothelial origin of erythrocytes in bone marrow. The endothelial origin of erythrocytes in bone marrow has not been confirmed; the claim is unsupported by the results of later studies, most recently that of McDonald [28] which shows the derivation of the erythrocytes in bone marrow of birds directly from

[28] McDonald, 1939.

of erythropoiesis and maintains this function in gradually diminishing degree to the time of birth. Meanwhile also the marrow of the developing bones assumes hemocytopoietic function and remains as the sole source of erythrocyte and granulocyte formation throughout postnatal life. Lymphocytes are supplied by the spleen and lymph nodes from approximately the end of the second month. Only the bone marrow will here be described in relation to blood development.

The ancestral tissue of all the varieties of blood cells is the mesenchyme. But mesenchyme is also the ancestral tissue of the several varieties of connective tissue, of fat and of smooth and cardiac muscle. What the differential factors are which determine that mesenchyme in a certain region shall develop into elastic cartilage, in another region into smooth muscle and in bone marrow into blood need not be discussed; the various answers are largely of the nature of speculations. The complete answer involves an explanation of embryonic differentiation and takes us back to the original zygote, endowed with all the developmental potentialities which find expression in the future adult body.

The problem of hemopoiesis begins with the second step, that following the stage of the parent mesenchyme. Here we begin to deal with a primitive blood cell, appropriately designated *hemocytoblast*. This cell represents a mesenchymal cell which has separated from the parent syncytium, withdrawn its processes and assumed a free condition and spheric form. This cell has certain differential features, including relatively large vesicular nucleus in which the chromatin is distributed in the form of minute granules. The nucleus contains one or several achromatic nucleoli. The cytoplasm of this cell is moderately basophilic. The hemocytoblast appears identical with the large lymphocyte. With proper technics, mitochrondria, Golgi net, segregation apparatus and cytocentrum can be demonstrated The several theories of blood development recognize this cell as the primitive blood cell. But they divide on the question whether these apparently identical blood cells are actually alike and as such, by reason of their multiple developmental potentialities, differentiate along specific lines into the several definitive varieties of blood cells under the impact of different specific environmental stimuli; or whether they are inherently different and specifically determined for development under the influence of a hereditary bias in spite of their apparent cytologic identity.

These differences of belief with respect to the nature of the ancestral blood cells are expressed in the several theories supported by different investigators: monophyletic (*unitarian*), diphyletic (*dualist*), triphyletic (*trialist*) and polyphyletic Adherents of the unitarian concept of blood development regard the hemocytoblast as the polyvalent ancestral cell of all of the varieties of definitive blood cells. The dualists recognize two genetically distinct blood cell ancestors, the *proerythroblast* ancestor of the erythrocyte line and the *leukoblast* ancestor of the leukocytes. A variation of the diphyletic concept recognizes an ancestral cell (*lymphoblast*) for the lymphocyte line, distinct from the common ancestor (hemocytoblast) of the red and white cells of the bone marrow. Under this concept the monocytes are variously included in either one of the two lines. The trialists recognize three distinct blood cell ancestors; one for the red cells, one for the

The prevailing monophyletic theory is that of Maximow,[29] the essential features of which are indicated in the following chart. Most of the indicated genetic relationships have already been discussed; only two of the included cells call for further description, namely, the "granule cell"[30] and the plasma cell.[31, 32]

MONOPHYLETIC CONCEPT OF BLOOD CELL ORIGIN

Bone Marrow

Hemocytoblast (lymphoid hemoblast—lymphocyte)

proerythroblast
("megaloblast")

↓

erythroblast

↓

normoblast

↓

erythroplastid
(reticulocyte)
(granule cell)

↓

mature red blood
corpuscle

↓

hematokonia

leukoblast
("myeloblast")

↓

granuloblast
("myelocyte")

↓

granulocyte
(granular leukocyte)

1. neutrophil
2. eosinophil
3. basophil

→ plasma cell
↓
Russell body cell

→ megakaryocyte
↓
platelets

→ monoblast
↓
monocyte

→ lymphoblast
↓
large lymphocyte
↓
small lymphocyte
↓
large lymphocyte
↓
small lymphocyte

The *granule cell* represents the final stage in the maturation of the erythrocyte. At the beginning of the erythroplastid level the red corpuscle is in the *reticulocyte* phase. Under normal conditions the peripheral blood contains approximately 0 5 per cent of reticulocytes. These cells are characterized by a residuum of basophilic substance in the form of threads and granules, demonstrable by staining with brilliant cresyl blue. *Polychromasia* of red blood corpuscles as seen in smears stained with Wright's stain is an expression of the presence of this same basophilic substance, and *punctate basophilia* is a modification of the same phenomenon. Following the reticulocyte stage, which has a duration of about three days, there occurs the granule stage. Granule cells occur in normal peripheral blood to the extent of about 0.5 per cent The specific feature of these cells is the presence of a refractive spheric body about 0.5 micron in diameter. The granule migrates to the periphery and is finally extruded, producing thus the mature erythroplastid. The significance of this granule is obscure; one might venture to suggest that it

[29] Maximow, 1909
[30] Isaacs, 1925.
[31] Marschalko, 1895.
[32] Maximow, 1928

stromal cells of the reticulo-endothelial system. However, in blood vessels of the yolk sac of mammals and along the mid-ventral area of the aorta of the human embryo of the second month, endothelial cells in small numbers do separate from the vascular lining and differentiate into erythrocytes.
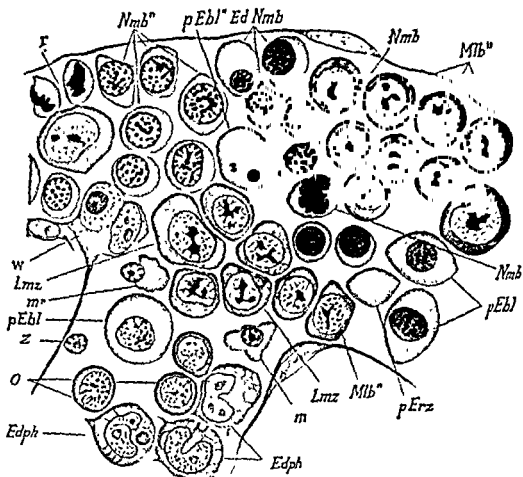
FIG. 240—SECTION THROUGH A BLOOD CHANNEL OF THE AREA VASCULOSA OF A 13½-DAY RABBIT EMBRYO, SHOWING EARLY STAGES IN BLOOD DEVELOPMENT.

Ed., endothelium, *Edph*, endot' ' ' ''emocytoblasts); *m"*, erythrocyte extruding its nuc ' ' ', young normo-blasts; *Nmb.*, older normoblasts, (iroblasts; *pEbl"*, enucleating erythroblast, *pErz*, erythroplastid, *r.*, dividing normoblast; *w.*, reticulum cell with ingested eosinophilic granulocyte, *z.*, extruded nucleus of erythrocyte. (Maximow, 1909.)

The essence of the monophyletic theories of blood cell origin inheres in the concept that myeloblasts, lymphoblasts, proerythroblasts and monoblasts are identical pluripotential cells. Myeloblasts and proerythroblasts are identical hemocytoblasts located in the bone marrow, the one in the intervascular stroma, the other within the venous sinuses. Lymphoblasts are identical hemocytoblasts located in lymph nodes and the spleen. Monoblasts are identical hemocytoblasts of spleen, marrow and lymph nodes which develop into phagocytic monocytes or macrophages.

into extranodular venous sinuses. Highly motile small lymphocytes migrate into the nodular capillaries and are swept into the venous sinuses. In these areas of virtual venostasis they grow into large lymphocytes, having the size and features of typical hemocytoblasts. In these leukostatic areas the hemocytoblasts differentiate into erythrocytes, the maturation proceeding in the direction from endothelial border to center of the lumen. Identical small lymphocytes also migrate out of the nodule into the intervascular stroma. Here they also grow into typical hemocytoblasts and subsequently differentiate into oxyphilic granulocytes. The evidence from avian bone marrow seems conclusive in verification of the monopheletic theory and in support of the claim that the small lymphocyte is a pluripotential embryonic cell, its subsequent differentiation being the result of the stimulus of a specific environmental factor. Within the venous sinuses these small lymphocytes (potential hemocytoblasts) enlarge and under the stimulus of a relatively high CO_2 tension differentiate into erythrocytes; in the intervascular stroma they differentiate into granulocytes. These findings in birds suggest that in mammals also an important function of the lymphocytes may be to serve as ancestral cells for the several varieties of blood cells. The explanation of the daily "loss" of approximately twenty-five billion lymphocytes in the human body may be that they are filtered out in the bone marrow where they become hemocytoblasts, supplementary to those locally produced to provide for the restoration of continually disintegrating erythroplastids and granulocytes.

BONE MARROW

The red variety of bone marrow, found in the flat bones generally and in the epiphyses of long bones, functions as the sole hemocytopoietic organ of later fetal and adult life. In certain mammals, e.g., opossum, hedgehog and bat, it is assisted in this function to some extent by the spleen. Besides a hemocytopoietic function, red bone marrow possesses also the capacity of destroying worn-out red blood corpuscles. In this process it is assisted greatly also by the spleen and lymphoid organs generally. The monocytes of these locations are the chief agents in this destructive process and in the transportation of the hemoglobin débris to the liver where as hematoidin it is apparently appropriated in the manufacture of the bile pigment, bilirubin. The proportion of red marrow to body weight in the normal adult man is approximately 5 per cent.[37]

The generic name for the specific hemogenic cells of marrow is *myelocyte*. This includes the parent blood cell (hemoblast, myeloblast) and the intermediate developmental stages of both white (lymphocytes, mononuclear leukocytes—leukoblasts) and red (proerythroblast, normoblast, erythroblast stages) cells. Besides these, there are of course abundantly present in marrow also the adult forms of blood cells both white (eosinophil, neutrophil, and basophil polymorphonuclear leukocytes, and lymphocytes) and red (erythroplastids). The term myelocyte in common usage is restricted to designate immature granulocytes. Potential osteo-

[37] Wetzel, 1920.

represents the archoplasm (centrosome) of the parent erythroblast. In the maturation process the nucleus is first extruded and then presumably the cytocentrum.

The *plasma cell* is a modified lymphocyte. Under the monophyletic concept the erythroblast also is a modified lymphocyte. As the erythrocyte passes from the initial hemocytoblast stage through the successive stages of erythroblast and normoblast (about five days' duration) the originally large vesicular nucleus gradually becomes smaller and more chromatic, the cell as a whole contracts and elaborates progressively larger amounts of hemoglobin. Mingled with the cells passing through this sequence of events in the bone marrow are occasional groups of plasma cells. With the exception of hemoglobin elaboration, these plasma cells pass through the same stages as outlined for the normal course of erythrocytogenesis, but in much more rapid tempo in the early steps. The nucleus of the parent lymphocyte (hemocytoblast) contracts very rapidly and in consequence eliminates a droplet of fluid into the cytoplasm. This process explains the characteristic feature of the typical plasma cell, namely, a juxtanuclear light-staining area or vacuole. The cytoplasm remains intensely basophilic by reason of the absence of hemoglobin. These cells apparently progress to no later stage of differentiation. But the possibility remains that these basophilic plasma cells may subsequently elaborate hemoglobin and so become indistinguishable from the more common erythroblasts derived along the more usual route. That the basophilic cells are still virile is indicated by occasional mitoses. However, in certain lymph nodes and the spleen, and under certain experimental conditions of lymphostasis,[33] apparently identical plasma cells undergo further changes: they lose their nucleus, either by intracellular resorption or by extrusion, in exactly the same manner as hemoglobiniferous normoblasts. They thus become basophilic plastids (basoplastids). The evidence suggests the conclusion that the plasma cells of lymph nodes and the spleen are definitively abortive erythroblasts,[34] and that those of normal bone marrow are atypical erythroblasts and normoblasts in which the nuclear changes outran the process of hemoglobin elaboration, thus producing transiently ahemoglobiniferous "normoblasts."

There remains for consideration the question of the significance of the lymphocyte. In the monophyletic scheme the large lymphocytes are considered identical with the primitive polyvalent blood cells, the hemocytoblasts. One aspect of this general question concerns the relationship between large and small lymphocytes. For solution of this problem the bone marrow of young birds supplies the most favorable material.[35, 36] Here lymphoid and myeloid tissues form an integral organ. Birds lack lymph nodes, but the bone marrow, especially that of the femur and tibia, contains scattered lymphoid nodules. With this arrangement *one may study the* relation of lymphocytes to the process of blood-cell production.

Arterioles supply a mesh of capillaries to these nodules; the capillaries drain

33 Jordan and Morton, 1937.
34 Jordan, 1929.
35 Jordan, 1936.
36 Jordan, 1939.

sive segregation apparatus. The monocytes arise in part also from reticulo-endothelium. They have a diameter of from 10 to 12 microns.

The chromatin is more generally arranged in strands, giving the nucleus a stringy appearance. Stained supravitally with neutral red, the cytoplasm is shown to contain a considerable collection of granules and globules. With Wright's stain
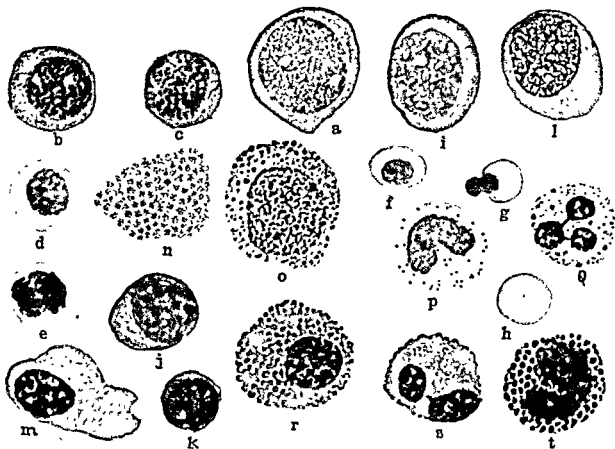
FIG. 242—SELECTED CELLS FROM MARROW OF THE STERNUM OF MIDDLE-AGED MAN.

a, hemocytoblast; b, proerythroblast ("megaloblast"); c, young erythroblast; d, later erythroblast; e, later erythroblast in mitosis; f, normoblast; g, normoblast with extruding nucleus; h, erythroplastid; i, large lymphocyte; j, medium-sized lymphocyte; k, small lymphocyte; l, monocyte; m, plasma cell; n, group of blood platelets; o, myelocyte; p, young neutrophilic leukocyte; q, polymorphonuclear neutrophilic leukocyte; r, young eosinophilic leukocyte; s, mature eosinophilic leukocyte; t, basophilic leukocyte. Smear preparation, Wright's stain. ×1500.

the cytoplasm of these cells, like that of lymphocytes and hemocytoblasts, may contain a variable collection of azurophilic granules. A cytocentrum is usually conspicuous, lodged within the depression of the frequently bean-shaped nucleus.

Polymorphonuclear Neutrophil Granulocytes.—These include a graded series of stages from the standpoint of shape of nucleus, and amount of granular content. The younger stages (myelocytes) contain a less complicated nucleus, generally bean-shaped with centrosome and relatively fewer (some basophilic, unripe) granules; these have a slight proliferative capacity. Older stages have progressively more complicated nuclei, characterized by a lobulated chain (with from two to five segments) of dense chromatin, and are no longer capable of mitotic division.

blasts and osteoclasts are also present, but indistinguishable from the lymphocytes and hemogenic polykaryocytes respectively unless specially stained.

A description of the cells in their order of hemogenic cytomorphosis follows:

Myeloblast (*Premyelocyte; Hemoblast, Mesameboid Cell; Primitive Blood Cell; Lymphocyte*).—This is the parent blood cell of bone marrow. It produces by proliferation and slight differentiation the more direct ancestors of both the white (leukoblast) and red (proerythroblast) cells. Mother and daughter cells
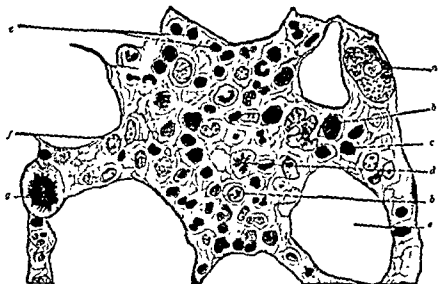
Fig. 241.—From a Section of Red Marrow of a Human Bone.

a, giant cell; *b*, leukocytes; *c*, nucleated red blood cells; *d*, mitosis in a marrow cell; *e*, outline of a fat cell; *f*, reticulum; *g*, mitosis in a giant cell. ×680. (Böhm and von Davidoff.)

are similar in their relatively large, finely granular, vesicular nucleus, well developed cell body, ameboid capacity, and proliferative activity. The cytoplasm of the myeloblast is homogeneous or very finely granular and slightly basophilic; likewise the leukoblast. The proerythroblast may be distinguished by its slightly oxyphil character due to the presence of a small amount of hemoglobin.

Lymphocytes.—These include larger, intermediate and smaller varieties. They are similar to, and in part identical with, the above-described cells, the myeloblasts. They include both cells differentiated from marrow and cells transported by the blood stream. In routine preparations they are indistinguishable from the osteoblast. In short, these several cells of similar characteristics may be identical in their capacity to function as progenitors of blood cells, and may represent parent blood cells. They range in size from 8 to 12 microns.

Monocytes.—These cells are distinguished from lymphocytes by their clearer nucleus, larger size and greater phagocytic activity. They represent lymphocytes specialized for phagocytosis. Transitional stages between lymphocytes and monocytes are abundant. Monocytes include the so-called large mononuclear and transitional leukocytes. Genuine transitionals between lymphocytes and granulocytes have a similar reniform nucleus, but they have a smaller size and lack an exten-

which segment into *blood platelets*. These blood platelets are abundantly present in red marrow.

Erythrocytes.—These cells include the several developmental stages of red cells: (*a*) proerythroblast, (*b*) erythroblast, (*c*) normoblast, and (*d*) erythroplastid. The proerythroblast is very similar to the leukoblast except that the cytoplasm contains a slight amount of hemoglobin, and therefore gives an oxyphilic staining reaction. The nucleus is finely granular, with a delicate chromatic network. This is the so-called ichthyoid stage of Minot. Normoblast and erythroblast are closely similar stages (sauroid stage of Minot), characterized by the relatively smaller and denser more chromatic nucleus, and a relatively more extensive shell of cytoplasm with increasingly more hemoglobin. The erythroplastid develops from the normoblast through loss of nucleus. This development occurs generally by extrusion, occasionally by resorption.

The stage here designated proerythroblast is the cell generally referred to in the literature as megaloblast. True megaloblasts, such as are characteristic of macrocytic anemia, do not occur in normal blood development. The proerythroblast stage of the original embryonic transitory line of red-cell development resembles the megaloblast of pernicious anemia, especially in size, but had better be called macro-erythroblast in order to distinguish it from true megaloblasts of certain anemias.

Macrophages.—These cells resemble large mononuclear leukocytes; they were first described by Metchnikoff in the year 1892. On the basis of a specific response to vital azo dyes Evans[39] identifies them as a group distinct from the large mononuclear elements and lymphocytes of the blood, and includes among them certain endothelial and reticular cells and the clasmatocytes (Ranvier) or "resting wandering cells" (Maximow) of connective tissue, all of which may become free macrophages. These cells in mammals, of round or elongated shape, range in diameter from about 10 to 30 microns; they contain a stoutly crescentic nucleus of irregular contour and excentric position; the cytoplasm is weakly basophilic, covered with delicate pseudopods of various sizes, and frequently filled with large vacuoles. As endothelial cells they line the capillaries and venules of the liver (von Kupffer cells), spleen, red bone marrow, hemal glands, and the lymphatic sinuses of lymph nodes. They include also reticular cells of lymph nodes, spleen pulp and bone marrow, and the clasmatocytes of connective tissue. As free cells they occur in the serous cavities, lymph sinuses of lymph nodes, spleen and hepatic capillaries. They are abundant in transudates and exudates in serous cavities. Only under pathological conditions do they appear in the peripheral blood stream. Weidenreich identified them with the large mononuclear leukocytes of the blood and lymph. Evans' experiments, on the contrary, give no indication that leukocytes are converted into these cells. They originate chiefly from endothelia. They constitute the *reticulo-endothelial system* of Aschoff (see p. 246). They are phagocytes and are active also in the normal physiological processes. They handle the blood and bile pigments, and fats and lipoids. The protoplasm of the macrophages is characterized

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[39] Evans, 1915

Eosinophil Granulocytes.—These cells resemble the neutrophils in their graded series of nuclear forms, ending in a lobulated polymorphous nucleus; but differ in the matter of size and staining capacity of the cytoplasmic granules. Normally the nucleus consists of only two, at most three, segments. The cytoplasmic granules are of fairly uniform size and of spherical shape, but much larger than the neutrophilic granules, and are strongly acidophilic, showing special affinity for the cytoplasmic stain, eosin. In the younger forms the granules are basophilic. The older types are identical with those of the blood. Again, only the less differentiated, those with oval nucleus and a centrosome, may divide mitotically.

Basophil Granulocytes.—These are identical with the *mast leukocytes* of the blood, but not with the mast cells of connective tissue.[38] They are characterized by a variable polymorphous nucleus, apparent lack of centrosome, extremely slight proliferative capacity, and presence of spheroidal nonuniform basophilic cytoplasmic granules. They are numerically increased in marrow and the circulating blood and in the spleen in certain diseases. At least in part they represent immature and aborted eosinophils.

Giant Cells or Myeloplaxes.—These are relatively enormous cells, of from 30 to 100 microns' diameter. They may have either a single large, frequently lobulated annular, nucleus (megakaryocyte) or occasionally several, even many, nuclei (polykaryocyte). The megakaryocyte is

FIG. 243.—MEGAKARYOCYTE (*M*) FROM BONE MARROW OF CAT, SHOWING FORMATION OF BLOOD PLATELETS (*p*) BY SEGMENTATION OF PSEUDOPOD WITHIN A VENOUS SINUS (*s*). (WRIGHT)

a derivative of the lymphocyte (myeloblast). The polykaryocyte represents a later modification of the megakaryocyte, the lobulated nucleus having become broken up into separate nuclei. These polykaryocytes (hemogenic giant cells) have been erroneously regarded as identical with the multinucleated osteoclasts. They are in fact potential erythroblasts, comparable to "blood islands," with only slight or no phagocytic capacity. With Wright's technic the cytoplasm of these cells presents fine purple granules. Osteoclasts do not contain such metachromatic granules. The polykaryocytes of the yolk sac of the 10-millimeter pig embryo can be seen to differentiate into erythrocytes, a hemoglobin-containing area developing about the several nuclei, the whole finally breaking up into an equal number of red cells. Giant cells are characteristic elements of all hemopoietic organs. The megakaryocytes protrude long pseudopodia

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38 Maximow, 1913

and granulocyte production of the primitive spleen, as represented in fishes, is apportioned in mammals among lymph nodes, spleen and bone marrow.

Red blood corpuscles (anucleate erythrocytes) are almost completely restricted to mammals. Certain submammalian forms, more prominently the urodele, Batrachoseps, have bloods with variable numbers of anucleate erythrocytes. With these exceptions, submammalian bloods contain only nucleated red cells. Blood platelets (thromboplastids) also are restricted to mammalian bloods. Correlated with the specific character of mammalian blood is a specialized character of the bone marrow inherent in the presence of megakaryocytes, the source of platelets. Submammalian bloods are characterized by the presence of an additional type of cell, the *thrombocytes* or spindle cells. The bone marrow of submammalian forms lacks megakaryocytes. Thrombocytes of submammalian bloods and megakaryocytes (platelet ancestors) of mammalian marrow are homologous cells Thrombocytes and platelets constitute sources of important elements in the mechanism of blood coagulation.

The evidence from comparative hematology suggests that the lymphocytes constitute common ancestral blood cells, the hemocytoblasts, from which are derived the several types of definitive, specific circulating cells: monocytes, erythrocytes and granulocytes. The proximal differential stimuli to differentiation along specific lines into monocytes, erythrocytes and granulocytes are respectively coarse tissue débris, particulate material and toxins, relatively high carbon dioxide tension (as in the venous sinuses of the bone marrow where blood flow is sluggish), and bacteria and parasites. The spleens of fishes with the fourfold function of lymphocyte, monocyte, erythrocyte and granulocyte production, furnish almost conclusive evidence of the ancestral relationship of the parenchymal lymphocyte to the several specific blood-cell products. The evidence from conditions in birds is equally convincing. Here the absence of lymph nodes receives compensation in the presence of large numbers of lymphoid nodules in the bone marrow. These nodules have an extensive capillary and sinusoidal vascularization. Small lymphocytes migrate into the intranodular capillaries and are carried into the extranodular venouses with almost static blood, where they grow in size and acquire the features of typical large hemocytoblasts and subsequently differentiate into erythrocytes. Similar small lymphocytes migrate from the nodules into the extranodular stromal areas where they also grow in size and acquire the features of typical large hemocytoblasts and subsequently differentiate into granulocytes. Similar small lymphocytes of splenic origin are filtered out of the blood stream in the bone marrow and undergo the same process of blood-cell maturation as the local nodular small lymphocytes.

This evidence from submammalian hemopoietic tissues suggests that in mammals also the large numbers of lymphocytes daily lost to the body (25 billion in man) are filtered out in the bone marrow to serve as ancestors for red and white cells. The lymphocyte is the universal blood mother-cell. It is an embryonic pluripotential blood cell, its future specific differentiation depending upon the type of stimulus it encounters; proximally, whether it continues sojourn in regions of sluggish blood flow as in venous sinuses or becomes halted in the extravascular stroma. Cytologic and embryologic evidence is completely negative to the claim that the small lymphocytes *represent* definitive cells, with specific unknown but important functions, comparable *to* conditions as regards erythrocytes and granulocytes. As derivatives from reticular stroma, lymphocytes constitute a portion of the reticulo-endothelial system. This system is the acknowledged source of macrophages (monocytes) and blood cells. The lymphocytes, properly interpreted, constitute the chief circulatory portion of the reticulo-endothelial system.

especially by its response to finely particular matter. Macrophages share the function of phagocytosis with the polymorphonuclear elements of the blood.

COMPARATIVE HEMATOLOGY

With minor exceptions among a few highly specialized or aberrant representatives of two invertebrate phyla (vermes and echinoderms), erythrocytes occur only in the blood of vertebrates. The exceptions include several glycerid and gephyrean worms and several sea-cucumbers among the echinoderms. In the invertebrates, with the exceptions noted, the respiratory pigment is dissolved in the plasma or body fluid and may contain respectively, iron as in hemoglobin and hemerythrin, copper as in the hemocyanin of certain arthropods and Mollusca, or vanadium as in ascidians.[40] In the craniate vertebrates the respiratory pigment is without exception hemoglobin. Two genera of gephyrean worms (Thalassena and Magelona) have anucleate erythrocytes. Lymphocytes occur throughout the animal kingdom. The same is true for monocytes, and with few exceptions, also for the several varieties of granulocytes.

The hemocytopoietic organ of invertebrates is the lining epithelium of the celom or some local aggregation of these cells. In the lower vertebrates, from fishes to amphibia, the chief blood forming organ is a spleen. In cyclostomes (hagfish and lamprey) the spleen comprises a highly vascularized lymphoid tissue, loosely and widely distributed in the wall of the intestine. The lymphocytes differentiate into erythrocytes within venous sinusoids, into granulocytes in the extravascular stroma. In the hagfish this loose hemocytopoietic tissue occupies a large part of the tunica submucosa throughout the lower portion of the intestine, and constitutes a *disperse spleen*. In the lamprey the blood forming tissue occupies the spiral valve, and occurs here as a *diffuse spleen*. In the case of lungfishes, the spleen is located in the wall of the stomach in the form of an *aggregate spleen*. In ganoids, elasmobranchs and teleosts the chiefly erythrocytopoietic spleen is extraenteral, sharply circumscribed and attached to the mesogastrium by a proper mesentery.

In these fishes the kidney plays a variable rôle, especially in larvel stages, in erythrocytopoiesis. Granulocytes may be formed also in the wall of the intestine as well as in the spleen and the kidney. In elasmobranchs granulocytopoiesis is largely limited to the subcapsular and general stromal regions of the gonads. In the urodele amphibia (salamanders) generally, red-cell production is restricted to the spleen; granulocytes are formed chiefly in the subcapsular region of the liver. In certain urodeles (Proteidae) the granulocytes are formed in the stroma of the kidney (mesonephros); the liver has no granulocytopoietic function. In the anuran amphibia (frogs and toads) the red cells are formed only in the spleen, except for brief periods following metamorphosis and hibernation when the bone marrow becomes transitorily active. Granulocytes are produced chiefly in the bone marrow, to a small degree in spleen and intestinal mucosa. In reptiles and birds, blood formation is carried on chiefly in the bone marrow; the spleen constitutes an accessory locus of erythrocytopoiesis of variable degree, relatively more intense in the early post-incubation months. The spleen constitutes the chief source of lymphocyte production.

In mammals, blood formation in the adult is restricted to the marrow. In fetal and progressively less in advancing infantile life, the spleen functions as an accessory organ of red-cell production, more intense in certain forms such as opossum and cat. Lymphocytes are produced in lymph nodes, thymus, spleen and to some degree in the bone marrow. With the exception of certain aquatic birds, where a pair of peculiar lymph nodes occurs in the region of the kidneys, lymph nodes are restricted to mammals. Phylogenetically considered, the fourfold function of lymphocyte, monocyte, erythrocyte

[40] Henze, 1932.

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CHAPTER IX

THE LYMPHATIC SYSTEM

The lymphatic series includes a system of lymphatic channels which collect the lymph from the various tissues of the body and return it to the large veins of the neck, where it mixes with the blood. In the course of this lymph vascular system are various aggregations of lymphoid or adenoid tissue which occur in the form of lymph nodules, lymph nodes and the lymphoid organs. These organs are the tonsils, thymus and spleen. The lymphatic vessels also stand in intimate relation if not in direct communication with the serous and synovial membranes and the bursae.

LYMPH

Like the blood, the lymph may be considered as a primary tissue whose intercellular elements are entirely of a fluid nature. In most portions of the body, lymph is a colorless fluid which is scantily provided with corpuscular elements, the *lymphatic corpuscles*. The lymphatic corpuscles are identical with the leukocytes of the blood. In the lymph most of these cells are of a mononuclear form, the small mononuclears or lymphocytes being the most abundant. Lymph also contains a small proportion of polymorphonuclear cells, which not only are derived from the lymphoid tissues, but as wandering cells find their way into the lymphatic vessels from the tissues generally. Blood platelets are not present in lymph;[1] thromboplastin is presumably liberated by the lymphocytes.

The cells of lymph, predominantly of the small lymphocyte type, are derived from the numerous lymphoid masses (nodes and nodules) through which the lymph passes on its way from the tissues to the subclavian veins. According to Davis and Carlson[2] the number of lymphocytes contributed to the blood daily may be more than the total permanently present in the blood. Since the number in a cubic millimeter remains fairly constant, a number must be daily consumed in the body equal to the number added to the blood. Many of course actually suffer destruction, but it seems probable that a considerable number also first undergo differentiation into granulocytes, and perhaps as potential hemoblasts may function as parent cells of erythrocytes. The peripheral lymphatics always contain some red cells.

A certain small number of lymphocytes migrate from the blood capillaries into

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[1] Howell, 1914.
[2] Davis and Carlson, 1909.

the tissue spaces and thence into the peripheral lymphatics. On the basis of this observation it is believed by some that the lymphocytes traverse a continuous and complete circulation involving in series blood capillaries, tissue spaces, peripheral lymphatics, thoracic duct and right lymphatic duct, superior vena cava, heart, arteries, capillaries. This would explain the apparent daily "loss" from the body of an enormous number of lymphocytes. However, if such circulation were actual fact, large numbers of lymphocytes, because of a necessarily slow progress through the tissue spaces, would pile up in the tissues, which is not normally the case. There is no rapid and extensive circulation of lymphocytes from blood to lymph. On the
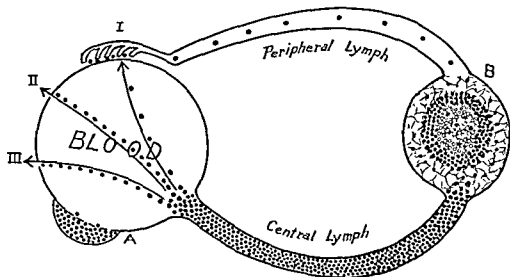
FIG 244—DIAGRAM OF THE VARIABLE FATE OF THE LYMPHOCYTE.

A, lymphoid tissues (*e g*, spleen) from which lymphocytes pass directly into the blood; *B*, lymphoid tissues (*e g*, lymph nodes) from which lymphocytes enter the blood indirectly *via* the lymph stream (thoracic duct). Along route I lymphocytes may pass from the blood to the connective tissues and thence to lymphatics, along route II they may pass through the intestinal mucosa to leave the body with the feces, along route III they may be filtered out in the bone marrow as potential hemocytoblasts. (Yoffey and Drinker.)

contrary it has been shown that out of every thirty lymphocytes entering the blood through the lymph stream, twenty-nine are newly formed and only one has entered the lymph from the blood.[3]

In addition to the leukocytes lymph contains fat globules and glycogen. These are mostly the products of absorption from the intestinal tract, in which process the lymphatic vessels play an important rôle. In the lymphatic vessels of the intestine during absorption fat globules are so abundant as to impart to the lymph a milky white color; this variety of lymph is termed the *chyle*. These fat globules are rapidly removed by the lymphoid organs, since even in the presence of abundant chyle only comparatively few fat globules escape into the general blood current. The lymph of other portions of the body than the abdominal region, therefore, contains relatively little fat.

[3] Drinker and Yoffey, 1939.

The lymph, unlike the blood, circulates in but one direction, *viz.*, toward the heart. It must therefore be formed in the tissues generally. The blood plasma constantly escapes through the walls of the capillary vessels into the surrounding lymphatic spaces of the tissues. It is these tissue spaces which have been considered as forming the beginning of the lymphatic system. However, the tissue spaces are not directly connected with the lymphatic vessels, but *just as the plasma exudes into the tissue spaces by processes of secretion, osmosis and filtration, so the tissue juices*, as the predecessors of lymph, enter the lymphatic vessels by similar processes of secretion, osmosis and filtration. Lymph is also formed by absorption, which occurs chiefly in the alimentary tract.

Under favorable conditions the lymph will coagulate, though more slowly than blood, the fibrin forming a firm, colorless clot in which the leukocytes are entangled. Because of their tendency to adhere to the sides of the vessel—thus circulating at the periphery of the current—the lymph cells are most likely to be found at the periphery in those postmortem clots which occur within the lymphatic vessels.

LYMPH VESSELS

The lymph vessels (*lymphatics*) vary in size from that of the smallest capillary vessels up to that of the thoracic duct. The smaller vessels, lymphatic capillaries, form anastomosing meshes in all tissues where blood capillaries are found. They are most abundant in the perivascular connective tissues, where they form a dense plexus about the wall of the blood vessels.

The wall of the *lymphatic capillary, like that of the blood capillary, consists of a single layer of endothelium.* This endothelium probably forms a complete lining for the lymphatic capillary and is continuous through larger and larger vessels with that of the veins, from which, according to Sabin,[4] the lymphatics are originally developed.

The relation of the lymphatic capillaries to the tissue spaces is not as yet definitely settled. It was formerly thought that these spaces were continuous with the lymphatic capillaries, but the observations of MacCallum [5] seem to show that the capillaries of the lymphatic system, like those of the blood vascular system, form a series of branching channels which are open only toward the veins. According to this conception, therefore, the tissue juices, formerly also considered as lymph, are contained within a separate series of channels, the tissue spaces and lymphatic canaliculi, and they enter the true lymphatics only by processes of osmosis and the secretory activity of the lymphatic endothelia.

The lymphatic capillaries are of rather irregular caliber, generally greater than that of blood capillaries, and possess frequent sinus-like dilatations, which peculiarity is also characteristic of the larger lymphatic vessels.

The lymphatic capillaries soon acquire an adventitial sheath of fibro-elastic

[4] Sabin, 1902
[5] MacCallum, W. G., 1903
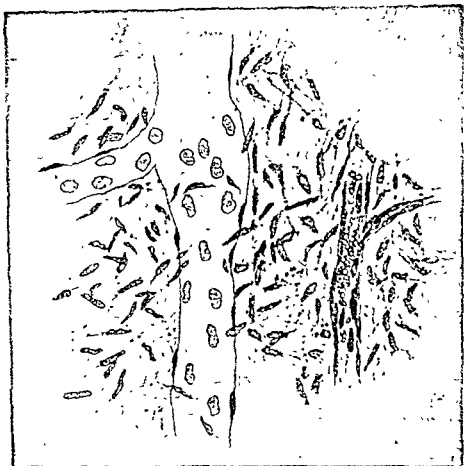
FIG. 245.—SUBCUTANEOUS LYMPHATIC VESSEL OF A FETAL PIG.
At the right is a small blood vessel. Highly magnified. (MacCallum.)

FIG 246.—THE GROWING END OF A DEVELOPING LYMPHATIC VESSEL IN THE SUBCUTANEOUS
TISSUE OF A FETAL PIG.

The lumen of the vessel has been filled with a dark injection mass. Highly magnified.
(MacCallum.)

tissue and pass into the *smaller lymphatic vessels*. On attaining a size of from 0.2 to 0.8 millimeter their wall is differentiated into the same three coats which are found in the veins. Except for the fact that they contain lymph instead of blood, these vessels closely resemble the small veins, and like some of the latter vessels they possess frequent valves.

The tunica intima of the lymph vessel consists of an endothelial lining with a thin delicate fibro-elastic membrane. The tunica media is thin and contains circular smooth muscle cells. The adventitia is the thickest coat of the lymph vessel.
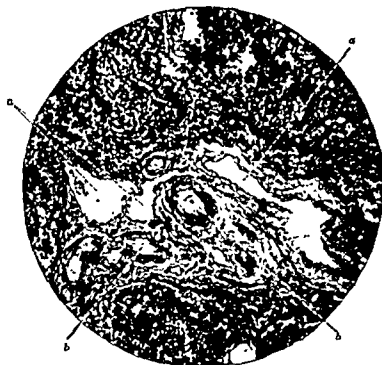
FIG 247.—LYMPHATIC AND BLOOD VESSELS IN THE HILUS OF A HUMAN LYMPH NODE. *a*, lymph vessels; *b*, blood vessels. Photo. ×160

It consists of fibro-elastic connective tissue and longitudinally disposed scattered bundles of smooth muscle fibers.

The wall of the lymph vessels is supplied with small blood vessels and nerves, in the same manner as the veins. The nerves form a plexus in the adventitia from which branches are distributed to the media and intima. Kytmanof has traced the fine nerve fibrils to the smallest lymphatic capillaries, where they end in close relation to the endothelial cells.

To summarize: the lymphatic capillaries arise by one of three methods:

1. As lymphatic plexuses in all connective tissues; the most abundant of these are the perivascular lymphatics.

2. As dilated pouches having blind extremities, as in the villi of the small intestine, where they are known as lacteals.

3 By direct communication with the stomata of the serous membranes. The

presence of true stomata in the serous membranes of man with the exception of possibly certain portions of the peritoneum is disputed.

The lymph is derived from the tissue juices and by absorption from the alimentary tract, and is conveyed by the lymphatic capillaries to larger and larger lymph vessels, which resemble the small veins in their structure, and which finally empty into the subclavian veins of the neck, at their junction with the internal jugulars

The main lymph channels are the *thoracic duct* on the left, and the right lymphatic duct. Only the thoracic duct drains the abdominal lymphatics and is thus much the larger vessel. Toward its distal end it expands into a receptacle for the absorbed chyle, the *cisterna chyli.*
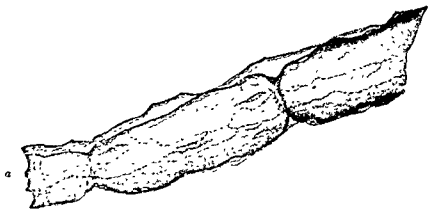
FIG. 248.—LYMPHATIC CAPILLARY FROM THE SPERMATIC CORD OF A DOG, SHOWING NERVE ENDINGS

Methylene blue. Highly magnified. (Kytmanof.)

Development.—According to Sabin the mammalian lymphatic system has its primary origin in two paired and one unpaired venous sprouts: the jugular, inguinal (sciatic), and mesenteric (retroperitoneal) lymph sacs. Certain investigators [6,7] interpret these sacs as the products of fusions of still more primitive discrete lymphatic primordia which arose as mesenchymal spaces; and their connection with the subclavian, sciatic and renal veins as secondary unions. Sabin and others regard the lymphatic endothelium once having sprouted from the venous endothelium as strictly specific, and the entire lymphatic system as a derivative by sprouting and fusion of these three sets of primordia.

Huntington and McClure derive the definitive lymphatic system by a progressive fusion of isolated mesenchymal spaces (mainly in the extraintimal portion of disappearing veins) and cells in the paths of the future lymphatic trunks. According to the one school lymphatic endothelium can arise only by proliferation of preëxisting endothelium; according to the other, endothelium can continually differentiate from young mesenchyma

The observations of Clark [8] on the growing lymphatics in the tail of living frog

[6] Huntington, 1911.
[7] McClure, 1912
[8] Clark, 1909.

tadpoles where the process of sprouting could be clearly followed, leaves no room for doubt that lymphatics spread through sprouting, but the material and data give no information as to the manner of origin of the initial primordia, which is the real question at issue. It is perhaps as yet too early to decide the matter on the basis of available evidence, but the extensive histologic data of Huntington and McClure strongly support their claim of primary lymphatic origin by confluence of isolated mesenchymal spaces.

The injections of Sabin which show a progressively enlarging continuous system in pig embryos apparently flatly contradict this hypothesis; but the objection cannot be fairly ignored that the advocates of lymphatic origin through fusion of isolated spaces base their claims on appearances before the establishment of a continuous system or even the several sets of lymphatic sacs, and the further fact that the injection method is unsuitable for revealing lymphatic primordia existing as isolated spaces. As concerns endothelium in general, Huntington [9] regards an endothelial cell as simply an adaptive form of a mesenchymal cell, "modified in accordance with definite hydrostatic and other purely mechanical factors," resulting from the presence of blood or lymph. On drainage of the fluid and consequent release of pressure, the endothelial cell is believed to be capable of again reverting to "the type of the indifferent mesenchymal cell." Kampmeier [10] presents evidence from a study of sections of the young toad embryo apparently demonstrating the primary origin of lymphatic endothelium only from venous endothelium; but the primary sacs and ducts arise by a confluence of these earlier discrete venous buds. A concise discussion and summary of this subject is given by McClure.[11]

SEROUS MEMBRANES

The serous membranes form closed sacs which line the great cavities of the body and are reflected over the viscera to form a double covering, the two layers of which are freely movable over one another. Of these two layers the one, the *parietal* layer, *is attached to the wall of the body cavity, the other, the visceral* layer, covers the surface of the inclosed organ.

The serous membranes consist of a *mesothelial lining* and a supporting membrane of areolar connective tissue which is richly supplied with capillary blood vessels and lymphatics. The mesothelium consists of large flat cells, pavement epithelium, whose serrated margins are firmly united by an intercellular cement substance. Here and there minute openings are seen which are surrounded by very small mesothelial cells; these *stomata* have been found to be in certain instances directly connected with the lymph vessels. Some regard them as transient fenestra, others as artifacts.

Lamina (Tunica) Propria.—The mesothelium rests upon a layer of areolar tissue which is richly supplied with small blood vessels and lymphatics, forming

9 Huntington, 1914.
10 Kampmeier, 1915.
11 McClure, 1915

an abundant vascular plexus beneath the mesothelium. The serous membrane is either directly united to the wall of the cavity and the surface of the organ which it envelops, or it may be attached by a loose layer of *submesothelial connective tissue*.
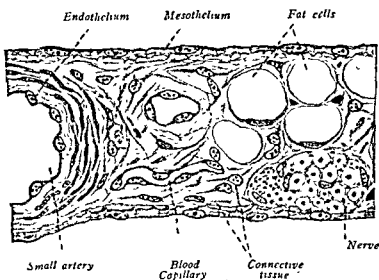
FIG. 249—VERTICAL SECTION OF MESENTERY OF MAN.
(Hardesty.)

FIG. 250.—SECTION OF A VASCULAR SYNOVIAL VILLUS
FROM THE KNEE JOINT OF A CHILD. ×200.

The thickness of the mesothelial cells varies in different portions of the serous membranes and is somewhat dependent upon the age of the individual. In most portions the membrane is no more than a pavement epithelium, but over the surface

of the functionally active ovary the cells are much thickened and acquire a cuboidal shape; thus it forms the "germinal epithelium" of the ovary. In young individuals, *viz.*, in fetal life and early childhood, the cuboidal cell type is found in many portions of the peritoneum, pleura and pericardium.

The *synovial membranes* resemble the serous in their structure. They are clothed by a single layer of pavement cells which may be incomplete in places. This epithelium (mesenchymal epithelium) is supported upon a layer of firm fibrous

FIG. 251.—A LYMPH NODULE, SOLITARY FOLLICLE, FROM THE LARGE INTESTINE OF MAN.

Migrating lymphocytes from the nodule have invaded the lamina propria of the mucosa.

tissue richly supplied with both lymph and blood capillaries. In the recesses of the joints the synovial membranes are frequently thrown into small villous folds, which are chiefly formed by the inner portion of the fibrous coat and are covered with epithelium; these are the *synovial villi*.

The *bursae* and the synovial sheaths of the tendons are of similar structure.

Both the serous and the synovial membranes are moistened by fluid which contains leukocytes in small numbers, and closely resembles the lymph and tissue juice in its composition.
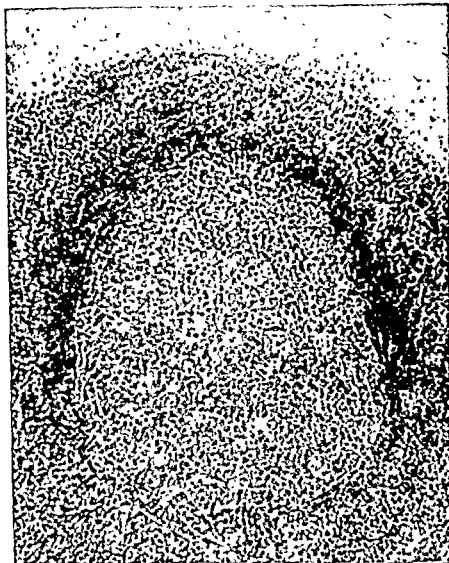
FIG 252 —MEDIAN VERTICAL SECTION OF SECONDARY LYMPHOID NODULE OF HUMAN LYMPH NODE.

The upper light half of the secondary nodule is the phagocytic zone, the lower dark half is the proliferative zone, the narrow dark border is the mantle zone of the primary nodule. ×66 (Kindred).

LYMPH NODULES

The lymph nodule (*lymph follicle*) is a structural unit of lymphoid tissue which may exist independently, as in the solitary nodules of the intestinal tract, or may form groups or accumulations consisting of a greater or less number of nodular units. In this latter condition they occur in the mucous membrane of the small intestine as Peyer's patches, in the tongue as the lingual tonsil, in the fauces as the faucial tonsils, in the pharynx as the pharyngeal tonsil, in the wall of the laryngeal cavity, in the spleen as the malpighian corpuscles (splenic nodules), in the lymph nodes as the peripheral lymph nodules, and in the thymus, where we may consider the lobule of the organ as being the structural equivalent of a lymph nodule.

The lymph nodule consists of a mass of lymphoid tissue, usually of ovoid form, which is surrounded by or embedded in connective tissue. In those locations where it exists independently the nodule is completely surrounded by the connective tissue in which it lies. In other places, as in the lymph nodes, the nodule is only partially surrounded by the connective tissue trabeculae of the organ. Not only do fine branches from the surrounding connective tissue bundles penetrate the periphery of the nodule, but the reticulum of the nodule is continuous with these trabeculae, thus forming a supporting stroma in which the lymphocytes are embedded.

The lymphocytes are loosely packed in the center of the nodule, and in this portion cell division by mitosis is most active. This central portion is the *germinal center* of Flemming, or *secondary nodule*. The germinal center is surrounded by a denser circumferential layer of lymphoid tissue in which cell division is less active. Between this denser portion and the surrounding connective tissue the lymphocytes are again more loosely packed, and over a greater portion of the nodule are separated from the trabeculae by a lacuna-like space, the internodular lymph sinus.

Rohlich [12] and Kindred [13] recognize in the secondary nodules of lymph nodes a distal light zone in which phagocytosis is the essential activity and a proximal dark zone (Fig. 252) where lymphocyte proliferation is relatively predominant. However, phagocytosis prevails in approximately equal degree throughout the nodule.

The nodule is usually supplied with a thin-walled artery, occasionally two, which penetrates to the middle of the nodule to form a wide-meshed capillary plexus. The capillaries, at the periphery of the nodule, unite to form two or more veins, which are contained in the adjacent connective tissue.

The *lymph cells* are mostly of the mononuclear type of leukocyte, the small mononuclear or lymphocyte type being the most abundant. Polymorphonuclear and eosinophil leukocytes are also found in the lymph nodules, though in much smaller numbers. Mitosis is most frequently observed in the large mononuclear type. Because of the nomadic tendencies of the leukocytes the boundaries of the nodule are not always sharp, the lymph cells frequently infiltrating the surrounding connective tissue so as to render it most difficult to distinguish the latter from the true lymphoid tissue of the nodule.

LYMPH NODES

Lymph nodes (*lymph glands*) occur in the course of the lymph circulation in various parts of the body. They are found in the neighborhood of the large joints, as in the axilla, the groin, the popliteal space, in the prevertebral and mediastinal connective tissue of the abdominal and thoracic cavities, and in the mesentery.

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[12] Rohlich, 1930.
[13] Kindred, 1937.

They are frequently in relation with the large arteries, *e.g.*, the renal and the internal and external carotids.

Each lymph node consists of a mass of nodular lymphoid tissue inclosed within a firm fibro-elastic connective tissue capsule. The capsule also contains a little smooth muscle tissue, but this is never so abundant as to form any considerable portion of the fibrous membrane; in fact, as compared with the somewhat similar capsule of the spleen, that of the lymph node is notably deficient in smooth muscle.

An *afferent lymph vessel*, pursuing its course within the capsule, enters the lymph node by a number of subdivisions which penetrate the deeper layers of the
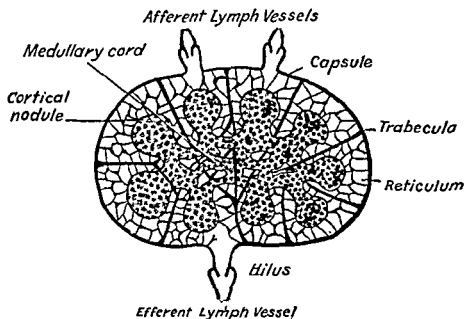
FIG. 253—DIAGRAM OF A LYMPH NODE.

capsule and open into a peripheral lacunar space, the *peripheral lymph sinus*, which separates the inner surface of the capsule from the adjacent lymphoid tissue, but which is bridged across at frequent intervals by the fine strands of lymph reticulum.

The lymphoid tissue, which forms the substance of the node, consists of a dense peripheral portion, the *cortex*, formed by closely packed primary lymph nodules, and a looser *medulla* in which are columnar accumulations of dense lymphoid tissue, the lymph cords.

Cortex.—The nodules of the cortex are partially separated from each other by septum-like trabeculae which extend inward from the fibrous capsule, and along which the peripheral lymph sinuses are continued into the substance of the node to partially surround its lymph nodules.

Each lymph nodule is thus surrounded, except at its central pole, by a peripheral lymph sinus, into which the afferent lymphatic vessels pour their contents. The lymph on entering the gland is thus permitted to enter the spaces of the reticulum and percolate through the lymph nodules of the cortex before it can reach the looser portions of the medulla. Each of the primary nodules of the cortex contains

a *germinal center* (secondary nodule) in which lymphocytes are actively formed by mitosis, and from which the lymphocytes readily escape along the lymph channels of the reticulum into the more open meshes of the medulla.

Medulla.—The medulla occupies the center of the gland, and at one point, the hilus, it reaches the surface. At this point a considerable mass of fibrous trabeculae enters the medulla, carrying with it the larger blood vessels to be dis-

FIG 254—TRANSECTION OF A MESENTERIC LYMPH NODE OF A MAN.
Hematein and eosin. Photo. ×38.

tributed to all portions of the gland. The finer ramifications of these medullary trabeculae are continuous with those of the cortex.

The lymphoid tissue of the medulla is divisible into the denser branching *lymph cords,* in which the lymphocytes are closely packed, and the intervening *pulp spaces,* or *medullary lymph sinuses,* in which lymphocytes are diffusely scattered.

The pulp spaces are broad channels, which are occupied by a reticulum whose meshes are partially filled with lymphocytes. They are bounded by a layer of endothelioid cells which everywhere incloses the denser lymph cords. The function of these cords is comparable presumably to that of the peripheral lymph nodules. The lining of the sinuses and pulp spaces constitutes a portion of the reticulo-endothelial system.

The pulp spaces are open toward the cortex, whence they receive the afferent lymph after it has percolated through the nodules, but toward the hilus the spaces are continued into the efferent radicles of the lymph vessels which, in the connective tissue of this part, unite into larger trunks, and finally form several efferent lymph vessels of considerable size

The *reticulum* of the lymph node is a close-meshed network of interlacing

fibrillar bundles, which are here and there clasped by flattened endothelioid connective tissue cells. Reticulum is but poorly stained with either acid or basic dyes, is destroyed by acids and bases, but is not digested by pancreatin. After prolonged action of Weigert's specific stain for elastic tissue it is but slightly colored.

Lymph nodes are subject to great variation. They are unstable structures; they apparently regress and regenerate according to need. The typical or ideal node is rare. Primary variation concerns the relation of cortex to medulla. On this basis lymph nodes may be classified as of two types.[14] In Type I the nodular portion surrounds the sinusoidal (medullary) portion, except at the hilus. In Type II the nodular and sinusoidal portions are lodged at opposite ends of the node; a peripheral sinus occurs only over the nodular portion. In certain nodes large numbers of lymphocytes of the medullary cords have become transformed into plasma cells Certain smaller nodes, especially in the submaxillary and cervical regions, consist predominantly of plasma cells. The cause underlying this extensive conversion of lymphocytes into plasma cells is unknown.

Lymph Cells.—The great majority of these cells are of the small mononuclear or lymphocyte type. Large mononuclear cells with a considerable cytoplasmic body are also very numerous Polymorphonucleated neutrophilic leukocytes, though of frequent occurrence, are less abundant than the previous varieties. Eosinophil cells are present in small numbers, and large basophilic mast cells are occasionally seen, though according to Carlier[15] they are mostly confined to the connective tissue. Drummond[16] also found large multinucleated giant cells, megakaryocytes, similar to those of the bone marrow; these were, however, very rare.

Fig. 255—The Blood Vessels of a Lymph Node.

A composite section of three nodules and the medullary cords of a mesenteric lymphatic node of the dog. A, artery; B, medullary artery; C, follicular vein; E, artery going to the capsule; F, capillaries in the periphery of a cord; G, medullary vein; H, nodular artery; I, arterial capillaries in a nodule; J, vein from capsule; K, cord; L, trabecula; V, vein. ×501. (Calvert)

Many of these cells, after proper fixation, show mitotic figures. This mitosis has been most frequently observed in the large mononuclear type, and is most abundant in the germinal centers of the nodules. The small mononuclear and polymorphonuclear types have also been shown to be capable of cell réproduction by indirect division. Reproduction by direct division of leukocytes appears to be rare.

The mononuclear as well as the polymorphonuclear forms are phagocytic.

[14] Job, 1922
[15] Carlier, 1893.
[16] Drummond, 1900.

Among the inclusions which have been found within these cells are fat globules, pigment granules, red blood corpuscles in partial disintegration, insoluble pigments, such as carbon granules, etc., and bacteria. The cells of the reticulum are also capable of phagocytosis.
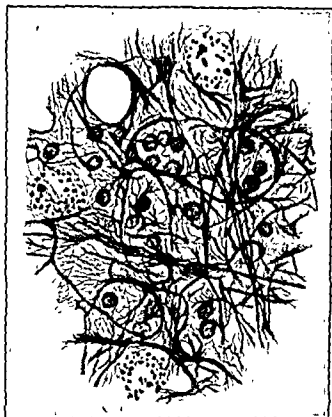
FIG. 256—RETICULAR TISSUE FROM LYMPH NODE OF RABBIT.

Tissue culture preparation after four days' growth. Numerous lymphocytes appear centrally. The coarser fibers are collagenous. Newly formed reticulum (argyrophil) fibrils subsequently change into collagenous fibers. (Maximow.)

Blood Vessels.—The arteries enter the lymph node at its hilus, and, following the trabeculae within which they lie, are distributed to all portions of the organ. In the medulla branches are distributed to the lymph cords, in which they form a wide-meshed capillary plexus.

The terminal branches of the primary divisions of the afferent artery are distributed to the nodules of the cortex. A single nodular branch [17] enters the nodule and passes straight toward its center, where it breaks into a plexus of divergent capillaries which unite at the surface of the nodule to form small venous radicles.

The veins follow the internodular trabeculae in their course toward the medulla, where they enter the medullary trabeculae, are augmented by venous radicles from

the capillary plexuses of this portion of the gland, and thence follow the trabeculae to the hilus, where they unite to form the efferent vein.

Certain of the arteries also pass from the medulla through the internodular trabeculae to the capsule of the gland, to which they supply a capillary plexus. The blood is returned through veins which retrace the course of the arteries and enter the large veins of the medullary trabeculae.

DEVELOPMENT

Lymph nodes arise through the invasion of primary lymphatic capillary plexuses by lymphocytes. The first lymph nodes arise in the regions of the axilla and groin during the third month of development. Such areas become circumscribed by the development of a capsule from the surrounding mesenchyma. The capsular tissue is continued into the developing node in the form of trabeculae, terminating in a dense network of delicate reticular fibers. Hydrostatic conditions probably determine the formation of a peripheral lymph sinus. The retention of certain channels (internodular and medullary sinuses) between the peripheral sinus and the efferent lymphatics at the hilus is likewise probably determined mainly by the operation of like factors, brought into play through the appearance of cortical nodules. These nodules arise as regions of proliferative activity of lymphocytes. The node has meanwhile early become invaded at a point which becomes the hilus by a vascular and nerve supply. Nodules arise as accumulations of proliferating lymphocytes about the cortical arterial twigs. Hemolymph nodes apparently arise in a manner similar to the origin of ordinary lymph nodes, and become only secondarily modified. The reticular tissue of lymph nodes may in part arise from the capillary endothelium.

The function of lymph nodes is the production of lymphocytes, which may become phagocytic leukocytes. Besides having a leukopoietic rôle, lymph nodes probably function also as centers for the dissolution of worn-out blood elements, in which process phagocytosis predominates, the lymphocytes being in part assisted by the reticulo-endothelial cells of the lymph sinuses. Lymphoid aggregations also serve as "lymph filters," the phagocytes removing from the lymph bacteria and other noxious products

HEMOLYMPH NODES

Hemolymph nodes (*hemal nodes*), which closely resemble the lymph nodes, were first described by H. Gibbes in 1884. He found them in the connective tissue between the renal artery and vein, in the human subject. They have since been found in the prevertebral connective tissue, in subcutaneous tissue, and in the mediastinum and mesentery. They are larger and more numerous in the ruminants, ox, sheep, etc., than in man. Their size varies from that of a millet seed to that of a pea In color they closely resemble a minute extravasation of blood.

These organs are essentially lymphatic structures in which the lymphoid tissue

is arranged in the form of cords rather than in nodules. The node is inclosed by a fibrous capsule, beneath which is a broad sinus filled with blood. In this fact, and also in the absence of lymphatics, lie the chief distinguishing features of these glands.

The *peripheral blood sinus*, which is analogous to the peripheral lymph sinus of a lymph node, sends into the interior of the organ a greater or less number of secondary sinuses. Based largely upon the abundance of these secondary sinuses, the hemolymph nodes have been divided into two varieties, named by Warthin [18] the "*splenolymph glands*" and the "*marrowlymph glands.*"
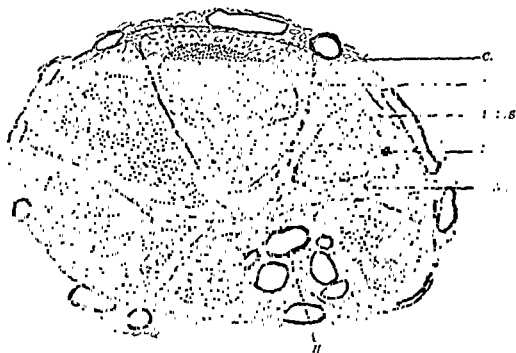
FIG. 257—SECTION OF HUMAN HEMOLYMPH NODE (SPLENOLYMPH GLAND).

C, capsule; *T*, trabecula; *P B S*, peripheral blood sinus; *L.T.*, lymphoid tissue, largely in the form of cords; *S B S*, secondary blood sinus; *H*, hilus. (Warthin.)

In the splenolymph type, which is the more abundant, the node is of small size and is well filled with secondary blood sinuses. The lymphoid tissue is supported by a similar reticulum, and contains the same varieties of lymph cells as in the lymph nodes.

In the marrowlymph nodes a somewhat similar structure is found. The blood sinuses are less numerous and lymph nodules do not occur (Vincent, Warthin). The eosinophil leukocytes and giant cells are more numerous than in the splenolymph type, and the marrowlymph nodes as a rule are the larger.

Huntington [19] has suggested that some of the structures described as hemolymph nodes may be postnatal hemocytopoietic foci, in which erythrocytes develop from

[18] Warthin, 1901.
[19] Huntington, 1914

the reticulo-endothelium of the lymph channels. They probably function as accessory spleens having a combined lymphopoietic, erythropoietic and phagocytic activity.

Intermediate types between the lymph nodes and the splenolymph type [20] on the one hand, and between the splenolymph node and the spleen and marrowlymph type on the other hand, are of frequent occurrence.

Hemal nodes are now generally regarded as modified or converted lymph nodes, the changes resulting from atrophy and disjunction of the lymphatics.[21] They may represent temporary stages in the regression and involution of transient lymph nodes.[22] Meyer,[23] however, considers hemal nodes as specific organs unrelated genetically to lymph nodes. He describes their separate origin in fetal mesenchyma. The peripheral blood sinus is said to develop *in loco,* independently of a vascular plexus. Arteries and veins only subsequently invade the node to establish the blood supply.

Blood Supply.—The afferent artery, according to Drummond,[24] enters the hilus with the connective tissue, and through the trabeculae reaches all parts of the node. In the lymphoid tissue its branches form a capillary plexus whose vessels open into the blood sinuses. The presence of blood in the sinuses is variously accounted for also as the result of extravasations from the capillaries and veins, and as the product of an erythrocytogenic transformation of lymphocytes. All the sinuses, peripheral and secondary, communicate with each other, and from them the blood is ultimately collected into two or more thin-walled veins. In the center of the gland these vessels unite to form an efferent vein which passes out at the hilus.

Weller [25] suggests the use of the designation hemolymph nodes as a generic term, applying the term hemal nodes to such as have blood vascular connections only, and hemal lymphatic nodes to those with lymph sinuses containing blood or with both blood and lymph sinuses. He evaluates the current data as supporting the conclusion that "Hemal nodes are certainly, and hemal lymphatic nodes are probably, organs *sui generis,*" as originally held by Warthin.

THE TONSILS

The Faucial Tonsils (Palatine Tonsils, Amygdalae).—The tonsils consist of a mass of *lymphoid tissue* which projects slightly from either side into the cavity of the fauces, and is covered by a layer of *stratified squamous epithelium* continuous with that of the oral and pharyngeal cavities. The lymph nodules which compose the tonsil immediately underlie the epithelial coat, and are embedded in areolar connective tissue. A thin capsule separates the tonsil from the underlying muscle.

[20] Vincent, 1897.
[21] Von Schumacher, 1912.
[22] Jordan, 1927.
[23] Meyer, 1917.
[24] Drummond, 1906.
[25] Weller, 1938.

The epithelial coat here and there penetrates the substance of the organ in the form of invaginated funnel-shaped depressions, the *crypts* (follicles of the tonsils), ten to twenty in number. The direction of the crypts in the upper third

FIG. 258.—VERTICAL SECTION THROUGH THE FAUCIAL TONSIL OF A MAN.

The crypts, two of which are shown opening on the surface, are lined with stratified squamous epithelium continuous with the mucous membrane. The white circular areas represent lymph nodules. The large black dots on the right and left borders represent striated muscle. (Hardesty.)
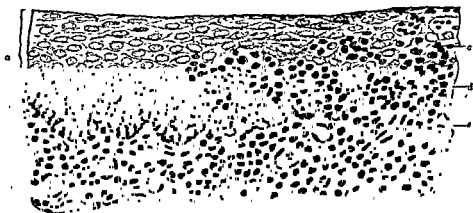
FIG 259—FROM A CRYPT OF A DOG'S TONSIL.

a, stratified squamous epithelium; *b*, basal margin of the epithelium; *c*, infiltration of the epithelium by leukocytes; *d*, spaces in the epithelium filled with leukocytes and epithelial cells; *e*, blood vessel; *f*, lymphoid tissue. ×150. (Bohm and von Davidoff.)

of the tonsil is downward and outward. The ducts of many mucous glands open into the recesses of these branching crypts. The mucus-secreting glands lie in the loose connective tissue which surrounds the tonsil on all but its faucial surface. The crypts are lined throughout by a layer of stratified squamous epithelium, which

is continuous with that on the free surface of the tonsil, but which becomes progressively thinner as it recedes into the deeper recesses of the crypts.

Many of the lymphocytes migrate into the intercellular spaces of the epithelial layer, and even penetrate to the free surface; thus they find their way into the oral cavity, where they occur in large numbers in the saliva, as *salivary corpuscles*. Within the superficial layers of the epithelium or within the crypts the nuclei of the lymphocytes tend to become polymorphous. Kingsbury interprets this as an incipient fragmentation and degeneration (*Am. J. Anat.*, vol. 75, 1945). If such salivary corpuscles are examined in a drop of saliva, freshly prepared, the fine intracellular granules of the polymorphonuclear leukocytes will be seen to undergo an active dancing movement, *brownian motion*. The salivary cor-

FIG. 260—THE LINGUAL TONSIL OF MAN.

a, a crypt; *b*, von Ebner's glands   × 45.

puscles are derived not only from the faucial tonsils but from the other lymphoid tissue which is in relation with the oral mucous membrane, *e.g.*, the lingual and pharyngeal tonsils.

The passage of leukocytes through the epithelial surface of the faucial tonsil is so very active that at times the epithelium becomes completely filled with these cells, and it is then difficult to distinguish it from the adenoid tissue beneath. The normal tonsils atrophy after puberty.

Although the tonsils are accumulations of lymphoid nodules these nodules are not surrounded by lymph sinuses and lymph does not filter through them. In this respect they resemble the lymphoid nodules of the spleen. However, lymphatic capillaries in the form of a plexus lie in the connective tissue between the external surface of the nodules and the epithelium. These channels connect with lymphatics from the dorsum of the tongue and drain into the superior deep cervical lymph nodes. The blood supply is from two sources, branches from the ascending pharyngeal and facial arteries enter its base and branches from the lingual and descending palatine arteries supply the mucous surface. A venous plexus communicates with the veins of the pharynx. The nerve supply is from a branch of the glossopharyngeal nerve.

The Lingual Tonsil.—A collection of lymph nodules is also found at the base of the

tongue in the median line, between the circumvallate papillae and the epiglottis. This, because of its similarity in appearance and in structure to the faucial tonsil, is called the lingual tonsil.

In the lingual tonsil, however, the nodules are grouped about a single *wide-mouthed crypt*, the *foramen caecum linguae*. This crypt is frequently branched, and into it the many mucous glands of the neighboring lingual mucosa pour their secretion.

The Pharyngeal Tonsil.—The posterior wall of the nasopharynx is supplied with a similar accumulation of lymph nodules, the pharyngeal tonsil. It lies in the median line and extends downward from between the orifices of the auditory (eustachian) tubes for a distance of three centimeters. It contains a considerable number of lymph nodules and several small crypts. The lateral extensions in the vicinity of the tubal orifices are sometimes known as the *tubal tonsils*.

The pharyngeal tonsil is prone to hypertrophy in youth, in which case it forms the adenoid growths which are common in certain children.

FIG. 261.—SECTION OF HUMAN SPLEEN.

The capsule, two attached trabeculae, and several splenic nodules with their artery, are well shown. ×240

Viewing the several tonsils and the associated lymphoid tissue as a whole, it will be perceived that they constitute a lymphoid ring at the gateway to the alimentary and respiratory tracts. The function of the lymphoid tissue is to produce phagocytic leukocytes for the protection of the body against bacteria and other noxious products. The tonsillar crypts offer favorable foci for the lodgment, invasion and attack of such harmful elements. The location of this annular mass of lymphoid tissue is significant; it is placed where it can apparently best perform a necessary function. When called upon to increase its functional activity lymphoid tissue responds by hypertrophy; this of itself may cause inconvenience by obstructing the channels employed in respiration and phonation. But when unable to respond adequately and thus successfully cope with the infecting material, the tonsils become diseased. This is commonly considered to call for removal of the involved lymphoid masses. Excised tonsillar tissue may be largely compensated for by regeneration and hypertrophy of other noninvolved lymphoid tissue.

THE SPLEEN

Structure.—The spleen is the largest lymphoid organ of the body. It is located to the left and dorsally between the stomach and diaphragm, has an irregular oval outline, measures about five inches in length and three inches in thickness, and weighs about seven ounces. It is subject to great variations in size and shape. It is enveloped by a thick, firm fibro-elastic *capsule*, or *tunica albuginea*, containing smooth muscle in its inner portion. The muscle provides for a slow, rhythmic contraction, about once a minute, assisting the flow of the blood. External to this is also a peritoneal investment, or *tunica serosa*. The capsule of the spleen of
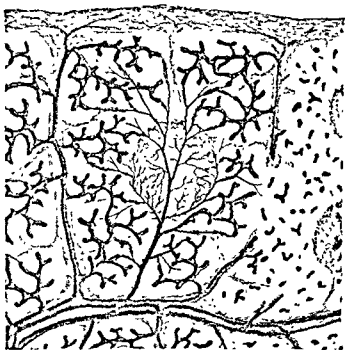
FIG 262—DIAGRAM OF CIRCULATION OF SPLEEN, REPRESENTED IN ONE PLANE.

The sinusoids are shown distended The right side of the illustration represents the abundance of sinusoids and arterioles as seen in sections. (Hardesty)

the ox is especially robust, and rich in smooth muscle At one point, the *hilus,* the capsule projects into the spleen as a large mass of trabecular tissue. Over the entire surface also other trabeculae project from the capsule into the parenchyma of the organ These trabeculae have a structure similar to that of the capsule. The supporting tissue of the parenchyma is a delicate reticulum. This is continuous with the fibro-elastic terminal processes of the fibromuscular trabeculae.

The primary trabeculae divide the parenchyma imperfectly into roughly pyramidal compartments about one millimeter in diameter, with three trabeculae for each lobule This lobulation is faintly indicated by surface markings. According to Mall this unit of structure, the *splenic lobule,* is further subdivided into about ten smaller compartments by anastomosing septa, continuous with the *primary*

splenic pulp. At first, and for a considerable distance, they follow an independent course through the pulp, receiving at the same time frequent accessions of blood from other venous radicles. Finally, however, the veins enter the larger trabeculae, but are still devoid of more complete coats than the thin membrane of fibro-elastic tissue which surrounds the endothelial tube, but which is now ensheathed by the trabecular tissue. Henceforth the path of the veins lies within the trabeculae (interlobular veins), and is directed toward the hilus. On approaching the hilus the larger veins acquire the usual venous coats. Having arrived at the hilus, they form several efferent vessels which, in the outlying connective tissue, form by
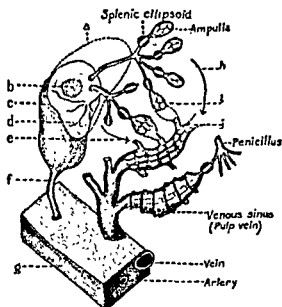
FIG. 265—VASCULAR SYSTEM OF THE SPLEEN. (ADAPTED FROM BRAUS.)

a, outline of complete splenic nodule, *c*, shown cut in transverse section; *b*, germinal center of nodule; *d*, capillary endings within the nodule; *e*, path of direct communication between artery and vein, *f*, extratrabecular artery entering a splenic nodule; *g*, trabecula; *h*, path of communication between fenestrated ampullary terminal of artery and open end of venous sinus; *i*, alternate possible course of blood through splenic pulp; *j*, free communication between pulp and venous sinus.

their union the splenic vein. The endothelioid lining of the arterial ampullae and the continuous venous sinuses belongs to the reticulo-endothelial system.

Microscopic observations of the terminal splenic circulation in unstimulated, living, transilluminated spleens of mice, rats and cats by Knisely [26] revealed the presence of "sensitive, powerful, reactive sphincters located at strategic positions" for the "precise, integrated control of the distribution of blood." The sheath of Schweigger—Seidel on the component arterioles of the penicilli are *described as* especially powerful sphincters. The other sphincter regions include the area of transition·from arterial capillary to venous sinus (afferent sphincter), transition from venous sinus to collecting venule (efferent sphincter) and the occasional con-

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[26] Knisely, 1936.

nection between two adjacent sinuses (Fig. 266). The sinuses progress from a collapsed conduction (post-storage) phase, when they resemble the pulp "partition" capillaries to successive "filling-filtration" phases, to the final storage phase, at which time the efferent sphincter closes Erythroplastids may pass in small numbers through the sinus wall into the pulp cords during the filling-filtration and storage
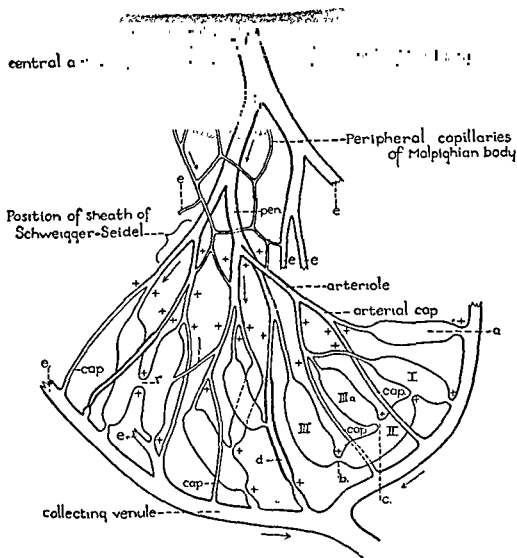
FIG. 266—COMPOSITE DIAGRAM OF TYPES OF VASCULAR CONNECTIONS OBSERVED IN LIVING SPLEENS OF THE RAT (Knisely, 1936).

I, II, III and IIIa, individual venous sinuses of a multiple sinus system, all in storage phase *a*, open efferent end of a single sinus route in early emptying phase; *b*, shows where efferent end of sinus III connects to afferent end of sinus II, *c*, shows where efferent end of sinus IIIa connects to side of sinus II; *d*, shows a venous sinus in conducting phase to distinguish it from pulp partition capillary, *e*, in different positions marks the end of the diagram; at each of these positions the blood vessels would connect to other blood vessels if the diagram were extended; *l*, arterial-capillary entering the side of a venous sinus; *r*, a rare type of connection between sinuses; *cap.*, the long relatively straight capillaries which extend lengthwise through the pulp partitions and end by connecting to venules Plus signs indicate the positions of the sensitive reactive physiological sphincters whose coordinated actions play so large a part in the control of the circulatory processes of the spleen

phases. The massive accumulation of erythroplastids in the pulp cords, characteristic of microscopical sections, is interpreted as the result of traumatic stimulation incident to the use of fixing fluids.

Solnitzky [27] interprets the ellipsoid as an integral part of the reticulo-endothelial system, a localized condensation of splenic pulp comprising reticular fibers and intensely phagocytic reticular cells. It contains neither smooth muscle, collagenous fibers nor elastic fibers. It has no active regulatory function. The axial vessel is a capillary with no preformed stomata.

Differentiation from Lymph Node.—The spleen in section can be readily differentiated from a lymph node; it lacks a definite subdivision into cortex and medulla characteristic of the lymph node, its pulp contains a preponderating number of red blood corpuscles and its capsule is relatively very robust and contains a greater amount of smooth muscle. The spleen may be thought of as a congested lymph node, consisting wholly of medulla, throughout which are scattered lymph nodules, the splenic nodules. It might quite properly be described as a huge hemolymph or hemal node.

Splenic Cells.—Besides erythroplastids and occasional erythocytes, the pulp contains also the several varieties of leukocytes: lymphocytes, granulocytes, a few megakaryocytes, and blood platelets. The leukocytes of the spleen are largely of the large mononuclear type (tissue monocytes). These are notably phagocytic, frequently containing erythroplastids, fragments of cells, pigment and other granular débris. They are in a sense specific for the spleen, hence called *splenic cells*. Megakaryocytes are abundant in the fetal spleen during its period of erythropoietic function, but rare in the adult spleen.

Lymph Supply.—The lymph supply of the spleen is relatively scanty. The capsular is independent of the trabecular system, which latter consists chiefly of perivascular lymph spaces and vessels draining toward the hilus. There are no lymphatics within the parenchyma.

Nerve Supply.—The innervation includes both myelinated and unmyelinated fibers. The latter predominate, and are distributed to the smooth muscle of the capsule, trabeculae and blood vessels.

Functions.—The spleen functions as a leukopoietic organ and as a blood filter. This is indicated both by the direct evidence of lymphocyte proliferation and the ingestion of erythroplastid débris by the splenic and reticulo-endothelial cells, and by the fact that the proportion of lymphocytes to erythroplastids in the splenic vein is very much greater than in the splenic artery. After severe hemorrhage or certain anemias the spleen may resume its fetal erythropoietic function. Numerous small supernumerary spleens, of varying size but usually about the size of a pea, are frequently found in the vicinity of the spleen.

Besides the production of lymphocytes and the destruction of senile red corpuscles, the normal adult spleen has been credited also with an erythrocytopoietic rôle and with a function concerned with the metabolism of iron. That the spleen does not, however, have any specific function absolutely essential to life is proved

27 Solnitzky, 1937.

by the fact that it may be removed without serious consequence. Obviously its function may be taken over by some other organs. Such compensatory rôle is usually attributed to the hemolymph nodes and the red marrow. However, splenectomy in dogs is not followed by increase in the number or size of the hemolymph nodes, nor by a production of accessory spleens.[28] Removal of the spleen in dogs seems to exert a stimulating effect upon the formation of red cells in bone marrow.[29] Pearse and Pepper [30] found that splenectomy caused a transformation of yellow into red marrow. The result is interpreted as showing that in the absence of the spleen the marrow may take on the function of storing and elaborating the iron of the blood pigment for future utilization by new red cells. The experiments of Austin and Pearse [31] on the contrary lead them to conclude that the spleen does not exert a constant and important function on iron metabolism. The complete function of the spleen apparently remains largely unknown. Like the thymus it is sometimes classified among the organs of internal secretion.

Barcroft *et al.*[32] have demonstrated that the normal spleen is usually much larger than that of the dead animal (dog, cat, rabbit and monkey). In the case of death from hemorrhage the living spleen is from two to five times its size after death. Similar changes occur after CO poisoning and drowning. During exercise also the spleen shrinks from 6 to 15 per cent of the blood volume. The view is advanced that "the spleen exercises a real function in adjusting the volume of circulating blood, or more correctly circulating functional hemoglobin according to the needs of the animal." This conclusion, that the spleen functions as a blood reservoir, receives further support from the experiments of Schunert and Krzywanek.[33] They have shown that while the number of red blood corpuscles in the dog increases from four million per cubic millimeter during rest to six million during exercise, no numerical change in the number of cells in the peripheral circulation occurs under similar conditions after splenectomy.

Development.—The primordium of the spleen appears at the beginning of the second month as a condensation and swelling in the mesenchyma on the left border of the dorsal mesogastrium. The overlying mesothelium proliferates extensively and its cells invade the mesenchyma obliterating the line of demarcation. The early histogenesis is obscure. The mesenchyma is potentially capable of producing all the definitive elements of the spleen: connective tissue capsule and framework, and lymphocytes The mesothelium, genetically closely related to mesenchyma, probably aids in the general process Probably also the bulk of the later lymphocytes invade the spleen from without.

THE RETICULO-ENDOTHELIAL SYSTEM

The designation *reticulo-endothelial system* was proposed by Aschoff as an inclusive term for widely distributed collections and derivatives of reticular con-

28 Meyer, 1914.   31 Austin and Pearse, 1914.
29 Krumbhaar, 1914.   32 Barcroft *et al* , 1925.
30 Pearse and Pepper, 1914   33 Schunert and Krzywanek, 1926.

nective tissue cells and of blood-vascular and lymph-vascular endothelium cooperating in the function of intense and frequent phagocytosis especially of senile blood elements, tissue débris and micro-organisms. As thus applied the term is one of great convenience, particularly in pathology. The reticulo-endothelial system includes the Kupffer cells of the liver, the splenic monocytes, the macrophages (see page 215), and the sinusoidal and capillary endothelium of the spleen, bone marrow, lymph nodes, hemal nodes, liver, hypophysis cerebri, and the suprarenals. It includes

RETICULO-ENDOTHELIAL SYSTEM
(Reticulo-endothelial or histiocytic metabolic apparatus)

· · · · · · · · · · ·.. ·. · ·... ., ·.·. · .–...ts)	*Histiocytic elements* (histiocytes) (migrating histiocytes)

Reticular cells of the	*Endothelial cells* of the	*Tissue histiocytes*	*Splenocytes*	*Blood histiocytes*
Splenic stroma Lymphatic tissue	Liver capillaries Lymph sinuses Splenic sinuses Suprarenal capillaries Hypophyseal capillaries			

Endothelial leukocytes   Histiofeukocytes

also the reticular connective tissue of these same organs and tissues, and of the thymus and tonsils. The various types of phagocytic cells, monocytes, macrophages, clasmatocytes, histiocytes, polyblasts, etc. (see page 50), have origin from these *endothelial and reticulum cells, or from the lymphocyte derivatives* of these parent cells. This system is believed to be the source of the fibrinogen of the blood. It is also concerned with blood destruction, the production of bile pigment and the storage and metabolism of iron, the *elaboration of antibodies* in defense against bacteria and protozoa, the removal of non-living foreign bodies, and probably in the metabolism of fats and proteins.

This matter is summarized in the above diagram, designed to show genetic relationships, adapted from Aschoff.[34]

The exact character of the lining of the intralobular capillaries of the liver, the venous sinuses of the spleen, the sinuses and intersinusoidal capillaries of red bone marrow and the lymphatic sinuses of lymph nodes, generally classified as important constituents of the reticulo-endothelial system, continues under discussion. The capilliform sinusoids of the suprarenal cortex and the pars distalis of

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[34] Aschoff, 1913.

the hypophysis cerebri also belong to this general group. Are these linings true endothelium, functionally modified for phagocytosis or are they histiocytic (reticular cell) membranes simulating genuine endothelium? Intravitam staining with colloidal dyes (e.g., trypan blue) and injections of suspensions of carbon granules and certain metals reveals a functional specificity among the cells of these endothelioid membranes: only a certain proportion of the cells, depending somewhat upon the size and number of repetitions of the dose, react phagocytically. Does this functional difference signify a certain phase of activity or a difference in origin of the cells of these lining membranes? True endothelia are normally not phagocytic.

In the case of the liver the phagocytic "endothelial" cells are the so-called cells of Kupffer. These are histiocytes, identical with the "stellate reticular cells" immediately beneath the endothelium and with the cells of the hepatic reticular stroma. An understanding of the relationship between the true endothelium of the intralobular capillaries, the associated cells of Kupffer, the subjacent stellate cells and the stromal reticular cells can be had from a consideration of earlier stages in the development of the liver. The branching biliary duct system of the liver, ending in the peculiar cell cords, invades the mesenchyme of the ventral mesentery. This process is coincident with an ingrowth and subsequent anastomosis of capillary branches from the vitelline and umbilical veins (later portal vein) and later from the hepatic artery and hepatic vein, the ultimate capillaries (capilliform sinusoids) flanking the cell cords. The original lining of the capillaries is true endothelium. The mesenchyme constitutes the reticular stroma. Histiocytes from this stroma migrate to the wall of the secondarily expanding capillaries and become incorporated as cells of Kupffer. Subjacent reticular cells become the so-called stellate cells. These histiocytes, whether as Kupffer cells, stellate cells or stromal cells, are phagocytes of the reticulo-endothelial system. The cells of the original endothelium of the capillaries are presumably the non-phagocytic cells of these capillaries.

Conditions in the lymph nodes are similar. The initial stage in the origin of a lymph node involves the invasion of a larger lymphatic by a tuft of capillaries; lymphocytes migrate from the blood stream of the capillaries into the surrounding mesenchyme.[35] Meanwhile sprouts from the original lymphatic grow into the accumulating mass of lymphocytes to become the initial medullary sinuses. The original lymphatic becomes the peripheral sinus; the reticular stroma arises largely from the perivascular connective tissue. The initial lymphatic sinuses of the node are lined with true endothelium. Coincident with a gradual enlargement of the sinuses, histiocytes migrate to the margin of the lumen to become incorporated with the lining "endothelium." These migrants into the wall of the sinuses constitute the phagocytic elements, namely, reticulo-endothelium. Other histiocytes migrate into the sinuses or persist during additions to the lumen of the sinuses, to constitute the sparse reticulum of these areas and to contribute macrophages.

The venous sinuses of the spleen pass through a similar course of enlargement by incorporation of true histiocytes among the non-phagocytic vascular endothelium.

[35] Kindred, 1940

nective tissue cells and of blood-vascular and lymph-vascular endothelium cooperating in the function of intense and frequent phagocytosis especially of senile blood elements, tissue débris and micro-organisms. As thus applied the term is one of great convenience, particularly in pathology. The reticulo-endothelial system includes the Kupffer cells of the liver, the splenic monocytes, the macrophages (see page 215), and the sinusoidal and capillary endothelium of the spleen, bone marrow, lymph nodes, hemal nodes, liver, hypophysis cerebri, and the suprarenals. It includes

RETICULO-ENDOTHELIAL SYSTEM
(Reticulo-endothelial or histiocytic metabolic apparatus)

Reticulo-endothelial cells (histioblasts)
(reticulo-endothelial system in the narrower sense: local histiocytes)

Histiocytic elements (histiocytes)
(migrating histiocytes)

| *Reticular cells* of the | *Endothelial cells* of the | *Tissue histiocytes* | *Splenocytes* | *Blood histiocytes* |

Splenic stroma	Liver capillaries			
Lymphatic tissue	Lymph sinuses			
	Splenic sinuses			
	Suprarenal capillaries			
	Hypophyseal capillaries	Endothelial leukocytes		Histioleukocytes

also the reticular connective tissue of these same organs and tissues, and of the thymus and tonsils. The various types of phagocytic cells, monocytes, macrophages, clasmatocytes, histiocytes, polyblasts, etc. (see page 50), have origin *from these* endothelial and reticulum cells, or from the lymphocyte derivatives of these parent cells. This system is believed to be the source of the fibrinogen of the blood. It is also concerned with blood destruction, the production of bile pigment and the storage and metabolism of iron, the elaboration of antibodies in defense against bacteria and protozoa, the removal of non-living foreign bodies, and probably in the metabolism of fats and proteins.

This matter is summarized in the above diagram, designed to show genetic relationships, adapted from Aschoff.[34]

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[34] Aschoff, 1913.

MUCOUS MEMBRANES AND GLANDS

The histologic structures which are necessary for the formation of a secretion include an epithelial surface, and a lamina propria of connective tissue which supports the requisite blood and lymphatic vessels and the controlling nerve supply. These structures may either form smooth membranous surfaces or apparent epithelial invaginations. The former are found on the surface of the mucous membranes, the latter are the secreting glands.

MUCOUS MEMBRANES

The mucous membranes may be said to include all those secreting surfaces which are directly or indirectly connected with the surface of the body, hence their epithelial clothing is continuous with that of the skin. The mucous membranes form the lining coat of the respiratory and alimentary systems, together with the ducts of their secreting glands; in the nose this membrane is continuous through the tear ducts with the conjunctiva of the eye and through the auditory (eustachian) tubes with the lining membrane of the middle ear. The broad expanse thus formed is known as the *gastropneumonic* mucous membrane. A second membranous sheet, the *genito-urinary* mucous membrane, lines the organs of the genital and urinary systems. It thus forms the lining membrane of the vagina, uterus, and uterine tubes; of the

FIG 267.—A MUCOUS MEMBRANE HAVING SIMPLE TUBULAR GLANDS.

a, artery; *b-b*, basement membrane; *C*, connective tissue; *d*, duct of the gland, lined with cuboidal cells; *E*, epithelium of the free surface with clear, columnar cells; *G*, lumen of the gland, lined with granular, serous secreting, columnar cells surrounded by secretory capillaries; *V*, veins. The arteries are striped, the capillaries and veins, black. Nerves are not represented.

urethra, bladder, ureters and pelvis of the kidneys; of the ducts and tubules of the prostate gland, the testes, and the smaller secreting glands which are connected with the genital system.

A mucous membrane consists of a superficial layer of epithelium of varying type, which rests upon a *basement membrane* (membrana propria) and is in turn supported by an investment of connective tissue, the *lamina propria*, or corium.

And there are indications that in the red bone marrow, the lining of the hemogenic and hemophagic venous sinuses contains contributions of histiocytes.

Under the term *hemohistioblasts* (Ferrata, 1914) are classified specific derivatives of the reticulo-endothelial system of hemopoietic tissues whose function is that of blood-cell formation, both red and white. The intermediate stage may again be a lymphocyte-like cell, the *hemocytoblast*. Depending upon the specific type of stimulus, these lymphocyte derivatives of endothelium or reticular connective tissue may differentiate either *into phagocytes or into red or white blood cells*.

MORPHOLOGIC TYPES

I. Tubular
- Simple
- Convoluted
- Branched
- Compound
- Compound tubulo-acinose (alveolar); racemose

II. Saccular (alveolar)
- Simple
- Branched
- Compound

III. Ductless glands; endocrine glands
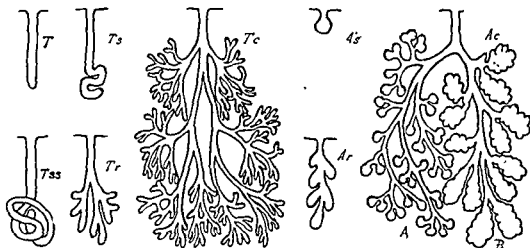
FIG. 268—THE PRINCIPAL TYPES OF GLANDS.

T, simple tubular (intestinal glands); *Ts*, slightly coiled tubular (intestinal glands and small sweat glands); *Tss*, more extensively coiled tubular (larger sweat glands); *Tr*, branched tubular (gastric glands), *Tc*, compound tubular (kidney, lacrimal glands); *As*, simple alveolar or saccular (small sebaceous glands), *Ar*, branched alveolar (larger sebaceous glands, tarsal glands of eyelid), *Ac*, (*A*) compound tubulo-alveolar or racemose (salivary glands); *Ac*, (B) compound saccular (mammary gland) In major part after Prenant, Bouin and Maillard.

Glands of the tubular and saccular types contain an actively secreting portion or *fundus* and a *duct*. Such externally secreting glands are also known as "exocrine" glands. In the ductless ("endocrine") glands the duct is absent. The duct, though its epithelium may take some part in the formation of the glandular secretion, primarily serves to convey the secretion of the fundus to the free surface of the mucous membrane.

The epithelium of the duct, as a rule, more or less closely resembles that of the mucous membrane upon whose surface it opens. The epithelium of the fundus, on the other hand, usually differs from that of the duct and varies according to the nature of its secretion. In many of the glands the epithelium is typically *mucus* secreting; others produce a clearer, watery, and less viscid *serous* secretion. Hence it is possible to distinguish the following:

PHYSIOLOGIC TYPES

I. Serous glands
II. Mucous glands
III. Glands which are both mucous and serous (mixed glands)
IV. Glands which are neither mucous nor serous

The lamina propria is richly supplied with small blood vessels and lymphatics; its nerve fibrils are not only distributed to the walls of the blood vessels but in many cases send terminal filaments which enter the epithelial layer and terminate in contact with the secreting cells. The mucous membranes are mostly contained within hollow organs which are subject to alternate collapse and distention; hence the membranes are frequently much folded. The deeper portion of a mucous membrane usually contains a more or less well-defined layer of smooth muscle fibers, the *lamina muscularis mucosae*.

The mucous membranes, as their name indicates, are nearly all moistened by a mucus-containing secretion. The relative amount of mucus which its secretion contains, and consequently the viscidity of the secretion, bears a close physiologic relation to the intensity of the mechanical irritation to which the membrane is subjected. Thus the mucus-secreting goblet cells of the gastropneumonic membrane are here and there reinforced by numerous mucus-secreting glands of considerable size. These are especially abundant in the oral cavity, pharynx, and esophagus, and in the nose, trachea, and bronchi. In the urinary system even the goblet cells are absent.

The basement membranes, upon which the epithelium of the mucous membranes and the secreting glands is supported, are connective tissue structures. They are sometimes formed by interlacing bundles of delicate collagenous fibers intermingled with numerous elastic fibers. Frequently, however, they consist of reticular tissue. Basement membranes of this nature have been demonstrated by Mall and his pupils in the mucous membranes and glandular tubules of the stomach, intestine, liver, salivary glands, kidneys, testes and thyroid. Certain basement membranes are homogeneous in structure and present a more or less hyaline appearance, *e.g.*, kidney.

GLANDS

The secreting glands may be quite properly considered as invaginations of the epithelial surfaces of the mucous membranes They appear as such in the embryo. Their earliest primordium is formed by a solid or funnel-shaped process of epithelium, in which a distinct lumen soon appears, and which grows into the surrounding mesoderm, carrying with it its embryonal tunica propria.

CLASSIFICATION

The form of the glandular invaginations is subject to great variation. They may be straight and simple, more or less branched and compound, convoluted or coiled, or the tubules may terminate in minute ampullary enlargements, the acini or alveoli. The invaginations may also be distinctly tubular and of approximately equal diameter throughout, or they may form pouch-like saccules. According to the form of the organ, it is thus possible to distinguish the following morphologic types:

with the varying character of their secretions, yet they present certain general characteristics. These cells are unquestionably capable of alternate phases of secretory activity and comparative rest. At the end of a period of activity they appear shrunken and small, and the lumen of their tubule is consequently increased in size. *Their nucleus is centrally located, and their cytoplasm is relatively devoid of secretion and frequently presents a faintly rodded or striated appearance.*

During *rest* secretion accumulates within the cell, and the cytoplasm consequently becomes either clearer or more granular, according as the nature of the secretion is watery, or is granular and zymotic in character; thus the secreting cells of the sweat glands become clearer as their secretion accumulates, whereas those of the pancreas become more granular.

As a rule the presecretion accumulates at the central end of the cell, the nucleus is thus crowded toward the basement membrane and is surrounded by
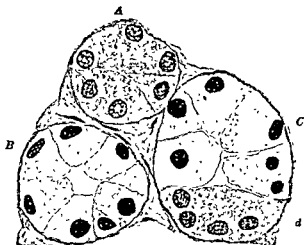
FIG. 269—TRANSECTION OF THREE SECRETING TUBULES OF THE SUBMAXILLARY GLAND OF MAN.
A, a serous tubule; *B*, a mucous tubule; *C*, a mucous tubule with a demilune, *d*, Hematein and eosin ×665.

the least altered cytoplasm. The whole cell becomes swollen and distended by the accumulated secretion and the tubular lumen is consequently diminished in size or even occluded.

Finally the period of *secretory activity* arrives, and the secretion is poured into the glandular lumen; the cells become shrunken and the lumen of the tubule correspondingly dilated. The cytoplasm returns to its former condition; if the secretion is of a granular character the cell becomes clearer, but if watery the cytoplasm acquires a finely granular appearance. The nucleus resumes its former central location and the cell enters upon a second period of constructive and accumulative activity.

Many of the serous-secreting cells contain minute *intracellular canals* which connect with a network of *intercellular passages* about the cell. The intercellular canaliculi may, on the one hand, open into the glandular lumen, or they may communicate with the tissue spaces of the lamina propria. *This system of intracellular and intercellular canaliculi may thus serve either as a system of nutrient*

This physiologic classification is not in any way the equivalent of the histologic gland types mentioned above. Thus both serous and mucous glands, in different locations, form almost every variety of tubular gland.

Description of Physiologic Types.—*Glands of the Fourth Type.*—The glands of the fourth type are too varied in their structure to be considered collectively to advantage. The reader is referred to the several chapters in which they are described in detail. This type includes the testes, the prostate, the ceruminous glands, the sebaceous glands, many of the ductless glands, and also some authors describe the ovary and the lungs as conforming to the glandular type of structure.

Mixed Glands.—The mixed glands include some tubules which are characteristically mucous, while others are typical serous secreting. Occasionally both types of secreting cells are contained within the same tubule.

Mucus-secreting Cells.—Mucus-secreting cells possess the general characteristics which have been previously recited under the head of goblet cells (Chapter II). When void of secretion the cytoplasm of mucous cells is granular, their nucleus centrally situated, and their shape more or less columnar. The presecretion accumulates in the central portion of the cell and occupies an area, adjacent to the glandular lumen, which steadily increases in size until the greater part of the cytoplasm has been replaced; the nucleus is pushed to the proximal or attached end of the cell; and the whole cell often becomes swollen and distended to more than double its original size. Finally the cell membrane ruptures and the mucus pours out upon the free surface of the membrane.

At the base of the mucus-secreting cells, and between them and their basement membrane, are groups of epithelial cells having a finely granular cytoplasm, which form crescentic cell masses, the *demilunes* of Heidenhain (crescents of Gianuzzi). In the tubules of some glands these demilunes are extremely minute, in others they occupy a considerable portion of the epithelial coat and encroach upon the glandular lumen. Their significance is not definitely understood. They have been considered as representing either secreting cells which are in a state of rest following the discharge of their secretion, or as *primordial cells which by reproduction give origin to true mucus-secreting cells.* It is quite possible that both of these functions are assumed by the several cells which compose the demilunes. Many of these cells contain an independent, intracellular, secretory, canalicular system, which indicates a specific and independent functional rôle.

Mucus, the product of the mucus-secreting cells, possesses peculiar properties. In the fresh condition it has a clear, glairy appearance and a pearly white color. Acted upon by alcohol or acids it gives a heavy precipitate of stringy white flocculi. Within the tissues these delicate flocculi stain slightly with basic dyes and readily with the muchematein and mucicarmine of Mayer. The very clear glairy appearance of the fluid and the slightly basophil properties of the precipitated flocculi are so characteristic that when typical mucus-containing cells are once carefully observed they can be thereafter readily distinguished from other types of epithelium.

Serous-secreting Cells.—Serous-secreting cells differ greatly in appearance

The typical *coil glands* consist of a duct whose epithelium resembles an attenuated layer of the stratified squamous epithelium upon which they open, and a fundus or secreting portion which is lined by columnar epithelium of the glandular type. They also possess a connective tissue basement membrane and a vascular lamina propria.

Branched Tubular Glands.—Branched tubular glands include the cardiac and pyloric glands of the stomach and the glands of the uterine mucous membrane. These glands possess a duct whose epithelium corresponds in type with that of the surface upon which they open. Several secreting tubules open into this duct by means of a short constricted portion, *the neck*. The fundus or secreting portion, after a typically spiral course, ends with a blind extremity which is often curved or hooked. This portion of the gland is clothed with columnar or glandular epithelium and invested with a thin basement membrane and lamina propria.

Compound Tubular Glands.—Compound tubular glands include the kidneys, testes, lacrimal glands and the liver. The finer structure of the glands of this type is so peculiar that the reader must be referred to the several chapters in which they are more fully described

Compound Tubulo-alveolar Glands (Tubulo-acinose or Racemose Glands).—This is the most widely distributed of all the types of secreting glands. It includes the parotid, the submaxillary, the larger mucous and serous glands of the oral cavity, and of the nose, pharynx, trachea, bronchi and esophagus, the duodenal (Brunner's) glands, the pancreas, bulbo-urethral (Cowper's) glands, urethral (Littré's) glands, and the large mucous glands of the cervix uteri.

FIG 270—MODEL OF A RECONSTRUCTION OF THE LACRIMAL GLAND OF MAN.

The tubular duct divides into the terminal secreting tubules, forming a compound tubular gland × 170. (Maziarski.)

The form of these glands may be likened to a much branched tree, whose stem as the main *excretory duct* opens upon the free surface of a mucous membrane, and the branches and twigs as the larger and smaller interlobular ducts reach out in all directions to end finally in minute alveolar dilatations, the secreting *acini*

Except for the ducts of certain mucous glands whose epithelial coat resembles that of the mucous membrane to which they are attached, the ducts of this type of secreting gland are lined by columnar cells whose cytoplasm frequently presents a rodded appearance at the deeper end of the cell. The acini contain typical serous or mucous, secreting epithelium. Occasionally the secreting cells are also found for some distance beyond the acinus in the lining membrane of the smallest ducts.

The tubules and acini of these glands are invested with a basement membrane and a delicate lamina propria. The acini are united by the connective tissue into small groups which inclose a central duct of the smallest type, the *intercalary* (or

channels or as a network of secretory capillaries by which the secretion is conveyed from the interior of the secreting cells to the lumen of the gland or even to the duct system. Secretory canaliculi of this nature have been demonstrated in the cells of the liver, the parietal cells of the glands of the stomach, the cells of the salivary glands, pancreas, adrenals, and epididymides. Nutrient canaliculi, in the form of so-called "trophospongium," occur in the cells of bladder epithelium and are highly developed in the nerve cells.

Glands may be classified also according to the method by which they elaborate their secretion: *holocrine* glands; *merocrine* glands. This terminology was proposed by Ranvier in 1886, and retains a certain value and convenience. Holocrine glands are such as suffer a destruction of their constituent cells in the process of forming the secretion. The sebaceous glands of the skin and scalp are notable examples. Here the secretion, the sebum, is elaborated by fatty metamorphosis, destruction and discharge of the gland cells. Merocrine glands are such as maintain the integrity of their cells during the secretion process, and retain the capacity for repeated function; *e.g.*, sweat glands. Glands in which the distal portion of the cells of the secreting epithelium *becomes detached or partially disintegrated* in the process of secretion, as in the mammary glands, may be designated *apocrine* glands.

DESCRIPTION OF MORPHOLOGIC TYPES

Simple Tubular Glands.—Simple tubular glands occur in the mucous membrane of the small and large intestine as the crypts of Lieberkühn or intestinal glands. In shape these glands resemble a test tube. They form straight tubules which open on the free surface of the membrane, are of approximately equal caliber throughout, and at their deeper end terminate in a blind extremity. The tubules are lined with epithelium and are embedded in a thin vascular lamina propria. Their epithelium includes the usual columnar and goblet cell types, the latter being more abundant near the mouth of the gland. Near the blind extremity are certain granular cells, the granules of some of which are slightly basophilic; other cells possess coarse granules which are highly acidophil, as demonstrated by Kultschitsky [1] in the intestinal glands of the dog, an observation which *is easily* corroborated for the simple tubular glands in the small intestine of man.

Convoluted Tubular Glands.—Convoluted tubular glands occur as the sweat glands of the skin, the ceruminous glands of the ear, and the glands of Moll in the eyelids. The above are typical simple coiled glands. Certain other glands, which are less typically coiled but are more or less convoluted near their blind extremities and are frequently branched, are also to be included under this type. Such glands are the pyloric glands of the stomach, and the small mucous glands of the oral and nasal cavities, pharynx, larynx, trachea, bronchi and esophagus. Some of these glands, and especially those of the pyloric end of the stomach, present terminal acinar dilatations, hence they also resemble to some extent a small tubulo-acinose type of gland.

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[1] Kultschitsky, 1897.

The typical *coil glands* consist of a duct whose epithelium resembles an attenuated layer of the stratified squamous epithelium upon which they open, and a fundus or secreting portion which is lined by columnar epithelium of the glandular type. They also possess a connective tissue basement membrane and a vascular lamina propria.

Branched Tubular Glands.—Branched tubular glands include the cardiac and pyloric glands of the stomach and the glands of the uterine mucous membrane. These glands possess a duct whose epithelium corresponds in type with that of the surface upon which they open. Several secreting tubules open into this duct by means of a short constricted portion, *the neck*. The fundus or secreting portion, after a typically spiral course, ends with a blind extremity which is often curved or hooked. This portion of the gland is clothed with columnar or glandular epithelium and invested with a thin basement membrane and lamina propria.

Compound Tubular Glands.—Compound tubular glands include the kidneys, testes, lacrimal glands and the liver. The finer structure of the glands of this type is so peculiar that the reader must be referred to the several chapters in which they are more fully described.

Compound Tubulo-alveolar Glands (Tubulo-acinose or Racemose Glands).—This is the most widely distributed of all the types of secreting glands. It includes the parotid, the submaxillary, the larger mucous and serous glands of the oral cavity, and of the nose, pharynx, trachea, bronchi and esophagus, the duodenal (Brunner's) glands, the pancreas, bulbo-urethral (Cowper's) glands, urethral (Littré's) glands, and the large mucous glands of the cervix uteri

FIG. 270—MODEL OF A RECONSTRUCTION OF THE LACRIMAL GLAND OF MAN.

The tubular duct divides into the terminal secreting tubules, forming a compound tubular gland ×170 (Maziarski)

The form of these glands may be likened to a much branched tree, whose stem as the main *excretory duct* opens upon the free surface of a mucous membrane, and the branches and twigs as the larger and smaller interlobular ducts reach out in all directions to end finally in minute alveolar dilatations, the secreting *acini*.

Except for the ducts of certain mucous glands whose epithelial coat resembles that of the mucous membrane to which they are attached, the ducts of this type of secreting gland are lined by columnar cells whose cytoplasm frequently presents a rodded appearance at the deeper end of the cell. The acini contain typical serous or mucous, secreting epithelium. Occasionally the secreting cells are also found for some distance beyond the acinus in the lining membrane of the smallest ducts.

The tubules and acini of these glands are invested with a basement membrane and a delicate lamina propria. The acini are united by the connective tissue into small groups which inclose a central duct of the smallest type, the *intercalary* (or

channels or as a network of secretory capillaries by which the secretion is conveyed from the interior of the secreting cells to the lumen of the gland or even to the duct system. Secretory canaliculi of this nature have been demonstrated in the cells of the liver, the parietal cells of the glands of the stomach, the cells of the salivary glands, pancreas, adrenals, and epididymides. Nutrient canaliculi, in the form of so-called "trophospongium," occur in the cells of bladder epithelium and are highly developed in the nerve cells.

Glands may be classified also according to the method by which they elaborate their secretion: *holocrine* glands; *merocrine* glands. This terminology was proposed by Ranvier in 1886, and retains a certain value and convenience. Holocrine glands are such as suffer a destruction of their constituent cells in the process of forming the secretion. The sebaceous glands of the skin and scalp are notable examples. Here the secretion, the sebum, is elaborated by fatty metamorphosis, destruction and discharge of the gland cells. Merocrine glands are such as maintain the integrity of their cells during the secretion process, and retain the capacity for repeated function; *e.g.*, sweat glands. Glands in which the distal portion of the cells of the secreting epithelium becomes detached or partially disintegrated in the process of secretion, as in the mammary glands, may be designated *apocrine* glands.

DESCRIPTION OF MORPHOLOGIC TYPES

Simple Tubular Glands.—Simple tubular glands occur in the mucous membrane of the small and large intestine as the crypts of Lieberkühn or intestinal glands. In shape these glands resemble a test tube. They form straight tubules which open on the free surface of the membrane, are of approximately equal caliber throughout, and at their deeper end terminate in a blind extremity. The tubules are lined with epithelium and are embedded in a thin vascular lamina propria. Their epithelium includes the usual columnar and goblet cell types, the latter being more abundant near the mouth of the gland. Near the blind extremity are certain granular cells, the granules of some of which are slightly basophilic; other cells possess coarse granules which are highly acidophil, as demonstrated by Kultschitsky [1] in the intestinal glands of the dog, an observation which is easily corroborated for the simple tubular glands in the small intestine of man.

Convoluted Tubular Glands.—Convoluted tubular glands occur as the sweat glands of the skin, the ceruminous glands of the ear, and the glands of Moll in the eyelids. The above are typical simple coiled glands. Certain other glands, which are less typically coiled but are more or less convoluted near their blind extremities and are frequently branched, are also to be included under this type. Such glands are the pyloric glands of the stomach, and the small mucous glands of the oral and nasal cavities, pharynx, larynx, trachea, bronchi and esophagus. Some of these glands, and especially those of the pyloric end of the stomach, present terminal acinar dilatations, hence they also resemble to some extent a small tubulo-acinose type of gland.

The typical *coil glands* consist of a duct whose epithelium resembles an attenuated layer of the stratified squamous epithelium upon which they open, and a fundus or secreting portion which is lined by columnar epithelium of the glandular type. They also possess a connective tissue basement membrane and a vascular lamina propria.

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Fig. 270—Model of a Reconstruction of the Lacrimal Gland of Man.

The tubular duct divides into the terminal secreting tubules, forming a compound tubular gland ×170. (Maziarski).

The form of these glands may be likened to a much branched tree, whose stem as the main *excretory duct* opens upon the free surface of a mucous membrane, and the branches and twigs as the larger and smaller interlobular ducts reach out in all directions to end finally in minute alveolar dilatations, the secreting *acini*.

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The tubules and acini of these glands are invested with a basement membrane and a delicate lamina propria. The acini are united by the connective tissue into small groups which inclose a central duct of the smallest type, the *intercalary* (or

intermediate) *duct.* These acinose groups are again united into the *lobules* of the gland by fine bands of connective tissue, and broader bands of loose connective tissue cement the many lobules into one glandular mass. The intercalary ducts by union within the lobule form numerous small *intralobular ducts* which approach the periphery of the lobule and at its margin open into the *interlobular ducts;* the latter are found in the broader septa of connective tissue between the lobules. The interlobular ducts by union with one another result in progressively larger branches which finally form the main *excretory duct* of the gland.

Simple Saccular Glands.—Simple saccular glands occur as the smallest sebaceous glands of the skin. These are small glandular pouches with a short duct, a constricted neck, and a dilated fundus which instead of having a single coat of epithelium as in most of the tubular glands, is more or less completely filled with a mass of epithelial cells. The cells as they approach the duct of the gland show progressive stages of degeneration and disintegration which culminate in the formation of a thick, viscid, fatty secretion. Since these cells form their secretion by disintegration they are obviously capable of passing through the various stages of secretory activity but once, and hence they must be renewed by the repeated mitotic cell division which occurs at the periphery of the saccule. Such glands are of the *holocrine* type.

The epithelium of the secreting saccule rests upon a distinct *basement membrane* and is invested with a very vascular lamina propria.

FIG. 271.—RECONSTRUCTION OF A MUCOUS GLAND FROM THE RESPIRATORY REGION OF THE NASAL MUCOSA OF A CHILD.

The duct passes directly into the secreting alveoli. A typical small tubulo-alveolar gland. ×200. (Maziarski)

Branched Saccular Glands.—Branched saccular glands include the larger of the sebaceous glands of the skin, in which several saccules pour their secretion into a common duct, and the tarsal (meibomian) glands of the eyelids in which a considerable number of saccules open into an axial canal by which the secretion is conveyed to the terminal duct. The structure of each glandular saccule of this type is identical with that of a simple saccular gland.

Compound Saccular Glands.—This type includes only the mammary gland. It consists of a system of tubular ducts which possess ampullary dilatations and many branches. Its ducts terminate in small saccular alveoli which have a thin epithelial lining. During the period of their inactivity the lining epithelial cells are much flattened and the acini appear shrunken. The epithelium of the *lactating* gland, on the other hand, is cuboidal or columnar, the height being more or less dependent upon the accumulation of secretion within the cell.

The secretion is formed in the same manner as in the tubular glands with an additional process of fatty infiltration by which fat droplets are formed within

the cytoplasm. These droplets collect in the central portion of the cell and are finally discharged into the lumen of the acinus with apparent rupture of the cell membrane and the escape of a portion of its superficial cytoplasm. The epithelium is thus capable of repeated secretion.

The mammary glands may be considered as offering an intermediate type between the branched saccular and the tubulo-acinose types. They may be classified as *apocrine* glands.

Ductless Glands (Endocrine Glands).—Under the head of glands it is necessary to consider certain structures which apparently contain secreting epithelium and which present a more or less distinct tubular arrangement. These bodies are the adrenals, thyroid, parathyroids, carotid glands, coccygeal gland, paraganglia, hypophyses cerebri, and epiphysis cerebri (pineal gland) These are also known as organs of internal secretion, or *endocrine* glands

While these glands do not possess an excretory duct, nevertheless some of them certainly, and the others probably, form certain products which find their way into the blood or lymph as so-called "internal secretions" or *hormones (autacoids)*. The epithelium of the glands may form either alveoli, tubules or solid cell columns, which are supported by very delicate connective tissue tunics. Many blood vessels, often of the thin-walled sinusoidal type, are found within these tunics and are thus brought into intimate relation with the epithelial parenchyma. In some instances lymphatics are distributed in a similar manner within the gland.

Fig. 272 —Reconstruction of an Intralobular Duct Dividing into Its Terminal Intercalary Ducts and Acini.

The terminal divisions of a large compound tubulo-acinose gland. The model was made from serial sections of the human pancreas. ×344. (Mazi-arski.)

The property of internal secretion is not peculiar to the ductless glands It has long been ascribed to the liver cells in connection with their influence upon nitrogenous and carbohydrate metabolism, and, in fact, many secreting glands, even though not of vital importance, are nevertheless found to influence the economy in certain ways which cannot be accounted for by the properties of their external secretions.

Finally, it must be emphatically stated that the types of secreting glands, as above described, are not bound by hard and fast lines, but many forms will be found which might well be placed under either of two or more types. Hence any classification of secreting glands becomes more or less arbitrary; nevertheless such a classification is of extreme importance as serving to establish in the mind of the student certain typical pictures with which individual glands may be compared, and important structural details will thus be noticed which might otherwise escape observation.

THE SKIN

The skin, or integument, consists of an outermost ectodermal layer of stratified squamous epithelium, the *epidermis* (cuticle), and a subjacent mesodermal layer of dense connective tissue, the corium or *derma* (derma vera, cutis vera), homologous with the lamina propria of the mucous membranes. The corium contains the nerves and the nerve end organs of special sense, and rests upon a subcutaneous layer of areolar and adipose connective tissue which, blending with fascia or periosteum, unites the skin to the underlying muscles and bones.

The skin serves a composite function: protection, regulation of body temperature, tactile sensation, and excretion. Its excretory rôle is accessory to the function of the kidney.

The skin is typically a stratified organ, and for convenience of description may be divided into the following layers:

Skin
- I. Epidermis
  - 1. Scaly layer
  - 2. Flattened cell layer
  - 3. Eleidin-containing layer; stratum lucidum
  } Horny layer; stratum corneum
  - 4. Granular layer; stratum granulosum
  - 5. Prickle cell layer
  - 6. Cylindrical cell layer
  } Germinal, malpighian or mucous layer
- II. Derma
  - 1. Papillary layer
  - 2. Reticular layer
- III. Subcutaneous tissue

THE EPIDERMIS

The epidermis (cuticle) or scarf skin serves for the protection of the more sensitive corium or "true skin." It is formed by a dense layer of stratified epithelium and varies in thickness in different portions of the body, being thickest upon those surfaces which are exposed to the greatest mechanical violence, *e.g.*, the palms of the hands and soles of the feet; and thinnest in the least exposed portions, *e.g.*, inner sides of the arms and the back.

The layer of stratified squamous epithelium composing the epidermis differs from that of the mucous membranes in that its superficial cells contain an abundance of keratin, a peculiar horny material. The production of keratin in the cells of stratified epithelium appears to be more or less dependent upon the desiccation which occurs in those cells which form the comparatively dry cutaneous surface. The cornification can scarcely be demonstrated in the stratified squamous epithelium of the moistened mucous membrane of the mouth and esophagus; it is present

though not pronounced in the partially moistened margins of the eyelids, lips, labia minora and glans penis. In the epidermis, however, cornification is pronounced and characteristic in all portions of the body.

The thickness of the cornified layers appears to be in proportion to, if not entirely dependent upon, the amount of mechanical violence to which the cutaneous surface is subjected. Accordingly, the increased thickness of the epidermis covering
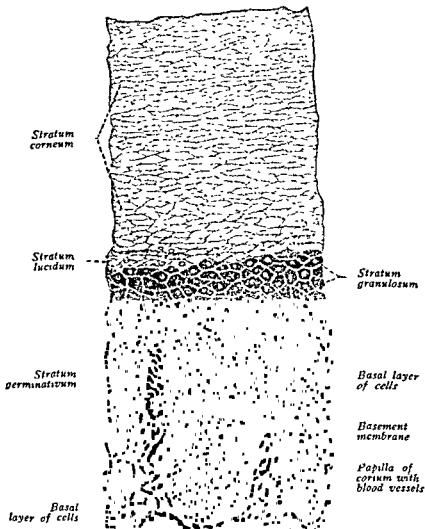
FIG. 273—EPIDERMIS OF SOLE OF FOOT. (Schneider.)

the palms and soles is found to be due almost entirely to an increase in the superficial horny portion of the epidermis, the germinal layers being no more pronounced than in other portions of the body.

The epidermal tissue is divisible into a superficial horny portion consisting of flattened, desiccated, cornified cells—the stratum corneum or horny layer—and a deeper protoplasmic, so-called "mucous" portion, which consists of polyhedral and cylindrical cells—stratum germinativum, stratum mucosum, rete mucosum, or rete malpighii.

Cylindrical Cell Layer (Stratum Cylindricum).—The deepest cells of the stratum mucosum are elongated in a direction nearly perpendicular to the basement

membrane upon which they rest; they are thus irregularly cylindrical in shape. It is these cells which in the pigmented portions of the body, *i.e.*, areolae of the nipples, scrotum, and circumanal region, and in the skin of brunettes and the colored races contain the pigment which gives rise to the darkened color of the skin.

In the skin of the Negro, the pigment (melanic) granules, while most abundant in the basal cylindrical cells, are nevertheless present, but in progressively smaller numbers, in all of the outer cell layers. In the various shades of mulatto skin, there is a close correspondence between the degree of color and the number of pigmented layers of epidermal cells. Certain connective tissue cells of the corium of pigmented skins also contain abundant melanin granules; in the darker skins such cells are numerous. However, the dermal pigment cells are not correctly regarded as the sources of supply of melanic granules for the epidermal cells, as has been maintained. The latter can produce their own granules; both dermal and epidermal
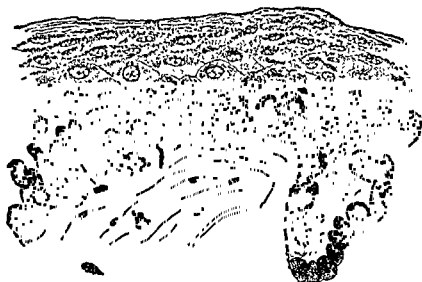
Fig 274—Section of Thin Skin from Abdomen of Negro, Showing the Distribution of the Pigment Granules in Dermal and Epidermal Cells. ×750.

pigment cells owe their condition to the same underlying cause.[1] The pigment granules are said to arise as a differentially staining nuclear substance (pyrenoid substance) which passes through the nuclear membrane into the cytoplasm, where it gradually acquires the character of pigment granules.[2] The nuclear origin of the prepigment granules is not confirmed. The more recent investigations indicate that the physiology of melanic pigment formation involves the interaction of a nuclear oxidase (tyrosinase) with an extranuclear, probably cytoplasmic, chromogen (tyrosin).

The processes of mitotic cell division are very active in these columnar cells, and they, with the adjacent portion of the prickle cell layer, form the *stratum germinativum* of Flemming, in which the regeneration of the epidermis occurs.

[1] Jordan, 1911.
[2] Meirowsky, 1908

The cylindrical cells are firmly united to the basement membrane by delicate cytoplasmic fibrils, the intercellular bridges. Their nuclei are ovoid in shape, and vesicular in appearance.

Prickle Cell Layer (Stratum Spinosum).—Superficial to the cylindrical cells is a stratum of polyhedral epithelium which extends inward between the adjacent papillae of the corium (*interpapillary region* of the epidermis), and is therefore thick in these portions, but is relatively much thinner over the apices of the dermal papillae (*suprapapillary portion* of the epidermis).

The polyhedral cells of this layer contain a soft granular cytoplasm and a vesicular, spheroidal nucleus. They are separated from one another by narrow intercellular spaces which are bridged across by innumerable delicate cytoplasmic fibrils. These fibrils connect adjacent cells and are frequently continued without interruption through one, two, or even three or four neighboring cells. Their course is characteristically curved, the convexity being directed toward the nucleus. Those portions of the numerous cytoplasmic fibrillae which span the intercellular spaces form the so-called *intercellular bridges*. It is because of the resulting spinous appearance that the polyhedral cells have been termed *prickle cells* (Schultze).
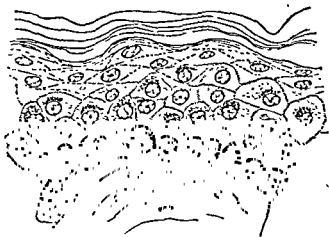
FIG. 275—SECTION OF THIN SKIN FROM ABDOMEN OF LIGHT BROWN MULATTO. ×750.

In the thinner portion of the epidermis the prickle cells are immediately covered by several layers of hard flattened cells whose nuclei have partially or wholly disappeared, and whose cytoplasm has been changed into a horny, keratin-containing mass. The flattening and desiccation of these cells becomes more pronounced as they approach the surface. In the thin portions of the epidermis the change from the prickle cell layer to the horny layer is abrupt.

In the thicker portions of the epidermis, as in the palms of the hands, the change is more gradual, and results in the appearance of two additional cell layers, in the cytoplasm of whose cells are intermediate products of chemical metamorphosis, keratohyalin and eleidin. These may be considered as the precursors of the keratin or *pareleidin* which is peculiar to the cells of the horny portion.

Granular Layer (Stratum Granulosum).—In the thicker parts of the cuticle the most superficial prickle cells become slightly flattened, and coarse granules appear within their cytoplasm. These cells form the granular layer (*stratum granulosum*), a double cell layer which occupies the superficial portion of the rete mucosum.

The cells of the granular layer are flattened and angular. They possess an indistinct, apparently degenerating nucleus, and their cytoplasm contains large

plate-like granules of *keratohyalin* (*eleidin* of Ranvier), which are strongly basophil and stain readily with most nuclear dyes.

Eleidin-containing Layer (Stratum Lucidum).—The granule cells are abruptly transformed into the shiny cells of the stratum lucidum, which is the deepest layer of the horny portion of the epidermis. The cells of this layer possess an indistinct nucleus, are irregularly flattened and angular in shape, are more or less fused
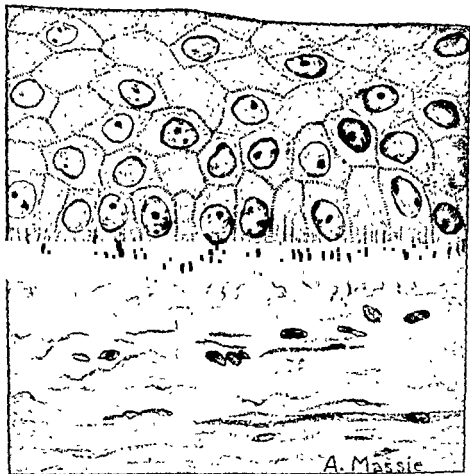
FIG 276.—VERTICAL SECTION OF THIN HUMAN SKIN, EXCLUSIVE OF STRATUM CORNEUM.

Note intercellular bridges among the several layers of cells. The columnar cells of the basal layer end in coarse processes ("denticulations," "striations") on the basement membrane. The processes contain coarse tonofibrils. ×1200. Iron hematoxylin stain

together at their adjacent margins, and contain a smooth, highly refractive, glassy cytoplasm which reacts feebly to most staining reagents, but is deeply colored by safranin.

The stratum lucidum is so named because of its highly refractive appearance; it is usually about two cells thick Its cytoplasm contains *eleidin*, a substance which is probably intermediate in chemical composition between the keratohyalin of the stratum granulosum and the keratoid pareleidin of the horny cells.

Flattened Cell Layer and Scaly Layer (Stratum Corneum and Stratum Disjunctum of Ranvier).—Above the stratum lucidum the horny layer consists of flattened cornified cells which are closely packed and somewhat fused and blended with each other at their faintly serrated margins. Intercellular bridges and spaces have almost entirely disappeared. The nuclei of the cells are no longer demonstrable, and their cytoplasm has been changed into a dry, shiny, highly refractive mass of *keratin* (pareleidin) which responds but slightly to ordinary stains. Its superficial layers stain deeply in osmic acid, indicating a considerable fatty altera-

Duct of sweat gland   *Ridges (rugae epidermis)*

Stratum corneum

Stratum lucidum

Stratum granulosum

Stratum germinativum

Meissner's corpuscle in papilla of corium

Basal columnar cells

Corium

Sweat gland

Fat in tela subcutanea
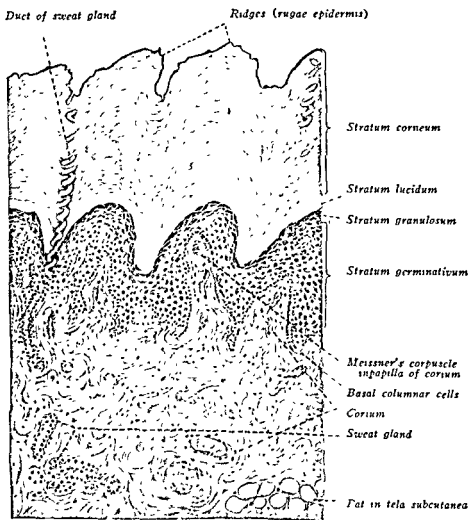
Fig 277—Skin from Palm of Human Hand (Hardesty.)

tion. If, however, these cells are acted upon by solutions of strong alkalis the outlines of the degenerated nuclei reappear. As the cells are pushed nearer the free surface, by the process of cell division in the deeper layers and the coincident desquamation of cells from the free surface, they become more and more flattened and desiccated and more completely and firmly fused together until at the surface *they form the partially detached cell masses or scales—*scaly layer, stratum squamosum—which are eventually removed by continued desquamation.

It is the thicker portions of the epidermis only, which possess all the charac-

teristic layers above described. In other portions of the body the horny layer is much thinner (Fig. 274). In these thinner parts the epidermis consists of a prominent rete mucosum which is covered by a relatively thin layer of horny cells. The stratum granulosum, in such portions, is not usually demonstrable, the stratum lucidum is absent or indistinct, and the entire horny layer consists only of flattened cornified cells, the more superficial of which form a thin scaly layer.

THE DERMA

The derma (dermis) or *corium* (derma vera, *cutis vera*) forms a connective tissue bed or matrix upon which the epidermis lies. It is divisible into two strata, a deeper reticular layer in which coarse fiber bundles interlace to form a loose connective tissue network, and a superficial papillary layer in which the finer bundles of connective tissue form a more closely meshed network.

The Papillary Layer (Stratum Papillare).—*The surface of the papillary layer presents numerous conical elevations, the papillae* of the corium, which project into corresponding cup-shaped cavities in the under surface of the epidermis. Many of the connective tissue papillae contain tactile end-organs (touch corpuscles of Meissner), and terminal filaments of the nerve fibers. They may therefore be regarded as the special organ of tactile sensation. Other papillae contain no touch corpuscles but are richly supplied with capillary blood vessels. Two types are thus distinguished, the *tactile papillae* and the *vascular papillae*.

Papillae are most abundant in the palms of the hands and the soles of the feet, where they are mostly arranged in rows which are responsible for the fine lines and ridges visible to the naked eye. In other portions of the body they are less numerous and are often less regularly disposed.

The papillary layer consists entirely of collagenous and elastic connective tissues which form a supporting membrane for the finer branches of the cutaneous blood vessels and nerves. The elastic tissue supplies a rich network of fine fibrils to all portions of the papillary layer, and just beneath the epidermis it forms a delicate elastic membrane whose fibers intermingle with the hyaline cuticular deposit of the columnar epidermal cells to form a firm resistant *basement membrane*. Many of the elastic fibers of the papillae, especially the more superficial ones, pursue a peculiar arciform course from the base to the apex of the conical papillae. In this way they surround and inclose the centrally situated capillaries and the tactile corpuscles of the papillae.

The Reticular Layer (Stratum Reticulare).—The deeper portion of the corium consists of interlacing bundles of connective tissue fibers which form a loose meshwork. These bundles are much coarser than those of the papillary layer with which they are imperceptibly blended. The reticular layer contains the larger blood vessels of the corium, many small nerve trunks, the ducts and parts of the secreting portions of the sweat glands, the more superficial sebaceous glands, and many of the smaller hair follicles. Lamellar corpuscles and nerve end-organs of Ruffini are also found in this layer.

The skin of the face contains many striated muscle fibers which are derived ·

from the insertions of the mimetic muscles. The corium of the scrotum (where it forms the tunica dartos), of the penis, perineum, and areola of the nipple contains much smooth muscle, intermingled with which is a considerable amount of elastic tissue.

SUBCUTANEOUS TISSUE

The subcutaneous tissue (*tela subcutanea*, *subcutis*, *hypodermis*) consists of bands and septa of fibrous connective tissue which extend from the deeper margin of the derma to the underlying fasciae of the muscles and the periosteum of the bones The direction of these fibrous bundles is very variable. The more nearly parallel to the cutaneous surface the fiber bundles are, and the looser the meshes which they form, the greater is the mobility of the skin

The meshes of the subcutaneous network are occupied by *lobules* of adipose tissue. When abundant the subcutis is termed *panniculus adiposus*. The subcutaneous tissue contains the main nerve trunks and larger blood vessels of the skin, the larger sudoriparous and sebaceous glands, and the coarser hair follicles. It also, together with the deeper part of the derma, contains the nerve end-organs of Pacini, Ruffini, and the Golgi-Mazzoni corpuscles (see Chapter VI).

Small bundles of smooth muscle fibers which form the arrectores pilorum muscles take origin from the deeper surface of the corium and are inserted into that portion of the hair follicle which is embedded in the subcutaneous tissue, usually slightly above the middle third of the follicle. An arrector pili muscle may comprise from two to five bundles. These fusiform or columnar muscle bundles are found in connection with all the hairs, but in the scalp they are most highly developed and lie most deeply in the subcutaneous tissue. However, in the scalp even coarser hairs may lack erector muscles.[3]

At the level of the vascular plexuses between the corium and the tela subcutanea, Häggquist[4] has described a thick bundle of smooth muscle not previously recognized It lies directly beneath a cold spot, and is not found in skin lacking cold spots The muscle is believed to contract reflexly when a cold object is placed on the skin and constrict the local blood supply.

In addition to the well-recognized functions of superficial protection and heat regulation, the skin serves also as a reservoir for the storage of cholesterol, water and sugar. Accordingly, it may play an important rôle in preventing dangerous desiccation after hemorrhage,[5] in carbohydrate metabolism[6] and in the effective utilization of ultraviolet radiations Eckstein and Wile[7] have shown that approximately one-fifth of the lipoid materials extracted from the skin consist of cholesterol Light treatment of the skin protects against rickets, apparently by activation of the ergosterol element in cholesterol. The cholesterol of the skin would seem to be mobile and serve an active metabolic function.

[3] Kanaizuka, 1926.
[4] Häggquist, 1913
[5] Skelton, 1927.
[6] Folin, Trimble and Newman, 1927.
[7] Eckstein and Wile, 1926.

DEVELOPMENT AND GROWTH

The skin may be said to arise with the first differentiation of the embryo into its three germ layers. The ectoderm, which is at first a single cell layer, becomes a double layer by the end of the first month. It continues to increase in thickness until by the end of the second month it can be differentiated into two layers, a superficial *periderm* (*epitrichium*), and a deeper *germinal layer.*

The periderm forms a layer of peculiar dome-shaped cells with flattened margins and a vesicular center. It continues to form the superficial layer of the epidermis until about the sixth month, when it is lost by desquamation. The germinal layer consists of a deep stratum of cylindrical cells and one or two superficial strata of spheroidal vesicular cells. The latter are known as the *stratum intermedium.* By the fifth or sixth month cell differentiation has advanced in the intermediate portion until cornification can be distinguished in its superficial cells.

Further development is analogous to the growth of the mature epidermis. New cells are rapidly formed in the deeper portion, stratum germinativum, and are steadily pushed toward the surface. Their migration is accompanied by slight, or later by more pronounced cornification. In the latter case this gives rise to the stratum granulosum, stratum lucidum, and horny layer. In the former case it produces only relatively slight flattening of the superficial cells without the appearance of keratin or the disappearance of the nucleus.

FIG. 278—THREE EARLY STAGES IN THE HISTOGENESIS OF THE SKIN.

A, single-layered epidermis from dorsal body wall of a 5 millimeter human embryo; *B,* two-layered epidermis from dorsal body wall of 13 millimeter human embryo; *C,* multiple-layered epidermis from nose of 21 millimeter pig embryo *Per,* periderm (epitrichium) ; *Ept,* epidermis; *Mes,* mesenchyma differentiating into the derma. ×750.

The derma arises from the superficial layers of the mesoderm as ordinary connective tissue, in which the appendages of the skin make their appearance as ingrowths from the epidermis Certain mesenchymal cells form the smooth muscle fibers of the arrectores pilorum muscles and of the derma of those locations where muscle is present in the mature skin. Other mesenchymal cells produce the fat lobules of the subcutaneous tissue. Papillae appear during the fourth or fifth month but do not attain their completed development until much later.

CUTANEOUS APPENDAGES

The *cutaneous appendages* include the sudoriparous glands, the nails, the hair, and the sebaceous glands.

SUDORIPAROUS GLANDS
(*Glandulae Sudoriparae, Sweat Glands*)

The sudoriparous glands occur in all portions of the skin, but more abundantly in certain locations, *e.g.*, palms of the hands and soles of the feet—where their number has been estimated at between two and three thousand to the square inch—axillae, groin, and circumanal region. Over the back, where they are least numerous, their number is said to be less than five hundred to the square inch. They are long, coiled or convoluted, tubular glands whose secreting portions lie in the subcutaneous tissue and in the deeper part of the corium. Their ducts extend through the corium to the under surface of the epidermis where the lining epithelium of the duct becomes continuous with the cells of the interpapillary portion of the stratum germinativum. In its further course through the epidermis the duct of the gland forms only a tortuous spiral cleft or passage whose wall is formed only by the concentrically placed cells of the various epidermal layers through which it passes. The glands of the axilla and circumanal region are branched.

The secreting or coiled portion of the gland (fundus) consists of a secretory epithelium resting upon a delicate hyaline membrana propria in whose outer portion are concentrically disposed connective tissue fibers. The inner portion of this membrane contains many longitudinal fusiform fibers whose nature is somewhat doubtful, though they have been most frequently considered to be smooth muscle fibers. They may be designated myo-epithelial cells. These cells are frequently branched, their processes often extending between the cells of the secreting epithelium nearly to the lumen of the gland.

The secreting epithelium of the fundus consists of tall columnar cells which possess a large spheroidal chromatic nucleus and a finely granular cytoplasm. The basal portion of their cytoplasm is often slightly rodded and the cells are so closely pressed together that it is frequently impossible to distinguish their outlines. The secreting cells are disposed in a single layer and, except after active secretion, are so tall as to leave only a very narrow, central, glandular lumen. During secretory activity the cells become shrunken and their cytoplasm more granular. After a period of rest the cytoplasm again becomes clear and vesicular in appearance and the cells are much distended. The secretion reaches the lumen through intra- and intercellular canaliculi.

The ducts are lined with a double, occasionally triple, layer of somewhat flattened epithelial cells, which rest upon a delicate membrana propria continuous with that of the secreting portion. The gross diameter of the duct is much less than that of the secreting portion of the gland, yet the lumen of the duct may be larger. That portion of the duct which is lined with the thin stratified epithelial layer pursues a spiral course through the subcutaneous tissue and the derma. It

finally reaches the epidermis, which it enters in the interval between the dermal papillae (interpapillary portion of the epidermis). Its lining epithelium is continuous with that of the stratum germinativum, and in its course through the epidermis the wall of the duct consists solely of the surrounding epidermal cells. The stratum granulosum and adjacent portion of the horny layer in the immediate neighborhood of the duct is invaginated into the stratum mucosum, which is thus considerably thinned by the passage of the duct.

The sweat glands are abundantly supplied with capillary blood vessels and small unmyelinated nerves, which form plexuses about the walls of the coiled portion of the gland, and from which terminal fibrils penetrate the basement membrane and end in contact with the secreting cells.

The sweat glands are not absolutely essential organs. The necessary insensible perspiration is mediated by the skin. The sweat glands constitute an emergency

FIG. 279—SEVERAL COILS OF A SUDORIPAROUS GLAND OF THE HUMAN FINGER.

a, secreting portions, their lumen containing traces of secretion; *b,* ducts; *m,* muscle cells ×550

apparatus called into action for the regulation of the body temperature only under stress of exercise, hot weather and the like.[8]

Development.—The sudoriparous glands first appear in the fetus during the fifth month as solid columnar ingrowth from the stratum germinativum of the epidermis. These processes grow inward through the primitive corium to its junction with the looser subcutaneous tissue. Here the cell columns become thickened and convoluted, and at about the same period their lumen appears. The glandular lumen is not at first connected with the free surface, but as the cells of the germinal layers of the epidermis gradually replace those which are more superficial the epidermal portion of the duct is formed. At about the seventh month the lumen of the duct opens upon the epidermal surface. The membrana propria of the

8 MacKee and Andrews, 1924

fundus and dermal portion of the duct is derived from the surrounding connective-tissue elements of the mesenchyma.

THE NAILS

The nails are produced by a peculiar modification of the epidermis by which the stratum lucidum becomes greatly thickened, while the horny layer (eponychium of the embryonic nail) is at the same time wanting. The nail is divisible into the *nail body* and *nail root;* the former comprising the exposed, the latter the hidden portion of the organ The root of the nail is overhung by a fold of the skin, the thickened horny layer at the margin of which forms an adherent border, the *eponychium* of the adult nail.

The nail groove or *sulcus* is included between the overhanging skin and the root of the nail. It is deep at its proximal end but is shallow at the lateral margins of the nail. The distal or free border of the nail projects over the skin at the tip

FIG 280—TERMINAL PHALANX OF FINGER OF HUMAN FETUS.

Showing *N*, nail; *F*, nail fold; *H* hyponychium; *E*, eponychium; developing sudoriparous glands, and developing bone.

of the finger and the thickening of the horny layer of the subjacent epidermis forms the so-called *hyponychium.*

Finer Structure.—The nail consists of two layers, the superficial stratum lucidum and the deeper germinal layer These are continuous at the border of the nail with the corresponding layers of the epidermis which lines the nail groove. At the distal border, however, the nail proper or thickened stratum lucidum ends in a free margin The finer structure of these two layers does not essentially differ from that of the corresponding layers of the epidermis.

The stratum lucidum in the body of the nail is very thick and its cells are so completely blended with each other through the excessive eleidin production

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that it is impossible to distinguish their outlines. By maceration in alkaline solutions, however, the outlines of both cells and nuclei may be caused to reappear. In the nail root the stratum lucidum increases rapidly in thickness as it grows distad; in the body of the nail this layer is not very materially thickened as it approaches the distal or free margin.

The stratum germinativum is of nearly equal thickness in all portions of the nail body. In the nail root it is somewhat thicker and forms the *nail matrix* of Ranvier. In this portion also is a distinct stratum granulosum, a layer which is absent or rudimentary beneath the body of the nail. It is the presence within this layer of *numerous keratohyaline granules which renders the root of the nail opaque and thus forms the dull white lunula* which contrasts with the transparent, eleidin-containing, *stratum lucidum, which* latter layer alone covers the germinal layer of the nail body.

Fig. 281.—Transection through the Margin of a Finger Nail.

On the left is the skin, on the right the nail. *a, a'*, horny layer; *b, b'*, germinal layer; *c, c'*, corium, *d*, margin of the nail; *s*, nail sulcus. Moderately magnified (von Brunn.)

The Nail Bed.— The nail rests upon a very vascular corium or nail bed (*matrix of authors*) which is continuous with the corium or derma of the skin. The nail bed is sometimes regarded as active in nail formation, but this process is now generally believed to be limited to the matrix of the root. The nail bed at the margins of the nail is provided with papillae as *in other portions of the skin*, but beneath the body of the nail its surface is raised into longitudinal ridges which possess only very minute secondary papillae.

Nail Growth.—The growth of the nail occurs in the matrix of the nail root. The cells of the stratum germinativum of this portion, having been once formed by active mitosis push obliquely forward and outward toward the nail
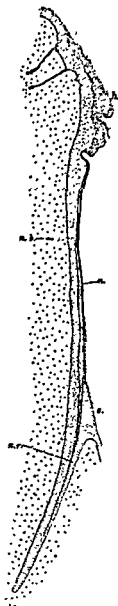
Fig. 282.—Longitudinal Vertical Section of the Young Nail and Nail Bed of an Infant.

n.r., nail root or lunula; *n*, nail; *n b.,* nail bed; *e.,* eponychium; *h*, hyponychium. (Dahlgren and Kepner.)

body. It is thus that the more advanced are constantly carried onward toward the free border. The growth of the nail occurs at the rate of about one thirty-second of an inch per week (Schafer).

Development.—In the fetus the nail appears as a direct formation of the epidermis, which is very early evidenced by a thickening of the stratum lucidum in the nail area. The nail is therefore at first covered by the superficial peridermal cells of the cuticle. The nail groove is rapidly formed by an invasion of the mesoblast by the epidermal cells which become piled up at the margin of the groove to form an excessive horny layer, the definitive representative of the embryonic eponychium. At the distal extremity of the nail the superficial cells are also accumulated into a considerable mass which forms a prominent hyponychium. Further growth of the nail pushes its distal margin forward over the hyponychium so that the border becomes free shortly prior to birth. The peridermal cells are then shed and the nail body finally presents, at about the time of birth, its naked stratum lucidum.

THE HAIR

Development.—The structure of the hair will be most readily appreciated if the discussion of the structure is preceded by a brief introductory sketch of its development.

The Hair Germ.—The hairs arise at any time after the third month of fetal life, their earliest primordium appearing as an area of slightly increased proliferation of the cells of the germinal layer of the epidermis. The further multiplication of the cylindrical cells produces a solid columnar ingrowth of the epidermis which penetrates into, and sometimes through, the primitive derma. The spheroidal cells of the intermediate layer of the epidermis increase in size, assume a vesicular character, and finally by fatty degeneration form the epidermal *hair canal* through which the future hair reaches the surface.

The Hair Column.—The columnar epidermal ingrowths, hair columns or hair pegs, come into early relation with the primordium of the *hair papilla* which is formed by a proliferation of the mesenchymal cells at the tip of the hair column. Further development of the papilla produces an indentation of the advancing hair column and gives rise to a true dermal papilla of considerable size.

The Hair Bulb.—Coincident with the formation of the papilla there occurs an increased proliferation of the cells of the hair column by which it is surrounded, and which therefore represents the future hair bulb. Two other swellings appear in the hair column; one, the more superficial, forming the primordium of the sebaceous gland, and the other, the deeper, forming the so-called epithelial bed or *matrix* of the hair which stands in close relation with the growth and future regeneration of the hair. This second swelling is sometimes interpreted as simply offering a point of attachment for the arrector pili muscle.

The development of the hair papilla produces a slight evagination of the epithelium of the hair bulb, which is just sufficient to redirect the growth of central cells of the hair column toward the cutaneous surface. It is thus that the younger cells
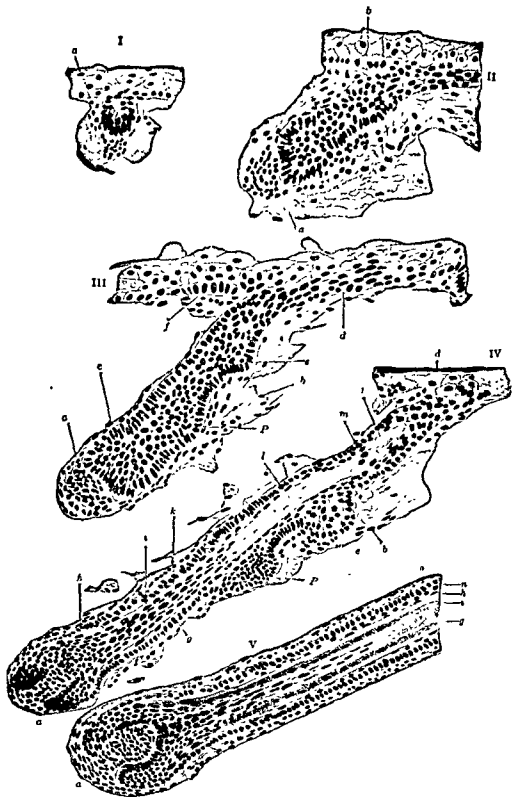
Fig. 283—Five Stages in the Development of a Human Hair.

a, papilla; *b*, arrector pili muscle; *c*, the line is directed toward the primordial shaft; *d*, cells which form the hair canal; *e*, sebaceous gland; *f*, hair germ in epidermis; *g*, hair shaft; *h*, Henle's layer; *i*, Huxley's layer; *k*, cuticle of the root sheath; *l*, inner epidermal root sheath; *m*, outer root sheath in tangential section; *n*, outer root sheath in longitudinal section; *o*, dermal root sheath; *P*, epithelial bed ×460 (Stöhr.)

which arise by mitosis in the germinal layers of the hair bulb are pushed outward along the axis of the hair column where they form the shaft of the future hair. The growth of the hair from the germinal cells of the hair bulb is accompanied by beginning cornification of the newly formed cells of the primitive hair shaft and of the intermediate cells of the hair column. The growth of the shaft is, however, preceded by enlargement, vesiculation, and fatty degeneration of the central cells of the hair column, thus producing a central canal through which the hair may grow, and which later becomes continuous with the hair canal of the epidermis.

The Hair Follicle.—At this stage the hair column has become differentiated into a peripheral follicle, the primitive *root sheath,* and a central *hair.* Continued multiplication of the cells in the germinal layer of the bulb pushes the advancing tip of the hair nearer and nearer the surface until it forces its way into the epidermal hair canal. Finally the thin cuticular covering is ruptured and the eruption of the *hair shaft* occurs.

Further differentiation of the cells of the epidermal root sheath and the formation of a mesenchymal or dermal sheath of connective tissue completes the development of the hair follicle. This process is frequently repeated and results in the formation of new hairs not only during fetal life, but also, in constantly decreasing numbers, throughout childhood and adult life.

The Mature Hair.—Its development reveals that the hair follicle, being formed as it were by an invagination of the epidermis, contains a dermal and an epidermal sheath and that the outer portion of the latter, being identical with the deeper portion of the epidermis, must possess a close structural resemblance to the rete mucosum, while its inner portion, like the horny layer of the skin, is more or less cornified. There is thus an outer and an inner epidermal root sheath corresponding respectively to the mucous and horny layers of the epidermis; the cornified portion, inner root sheath, becomes progressively thinner toward the hair bulb. The hair, on the other hand, represents an excessively developed horny layer whose rete mucosum is found in the germinal layer of the hair bulb.

The mature hair is divisible into a *hair shaft* or free portion, and a *hair root* or concealed portion. The latter is inclosed within an epidermal and a dermal root sheath which together form the hair follicle.

The Hair Shaft.—Sections of the hair shaft present a thin cuticle which consists of delicate horny scales whose free edges are imbricated upward, *viz.,* toward the tip of the hair. Within the cuticle the hair may consist solely of a hair *cortex* formed by flattened and very much elongated horny epithelial cells, which frequently retain the remnant of a nucleus, and whose keratized cytoplasm is often much pigmented; or the axis of the coarser hair may contain enlarged angular cells in which eleidin granules and much pigment are found. In the latter case the hair is said to possess a *medulla.* The medulla is seldom if ever present throughout the entire length of the hair. When present it sometimes contains numerous air bubbles which, together with the paucity of pigment, produce the lighter shades of hair peculiar to certain individuals. Whitening of the hair is the result of the

activity of pigmentophages (Metchnikoff, '98), macrophages which invade the periphery of the hair bulbs and absorb and digest the pigment granules.

In the light of its development it is obvious that the several layers of the hair shaft are comparable to the homologous layers of the horny epidermis, the cuticle, cortex, and medulla of the hair being respectively homologous with the scaly layer, the flattened cell layer, and the eleidin-containing layer or stratum lucidum of the epidermis.

The Hair Root.—The root of the hair, except for the fact that it is immediately invested with a hair follicle, does not in any way differ in structure from the hair shaft. It possesses the same three layers, the medulla, however, being very irregularly developed.

The imbricated cells of its cuticle interdigitate with the similar cells of the cuticle of the inner root sheath in the deeper half of the follicle; in its superficial half, *viz.*, above the opening of the sebaceous gland, a narrow space intervenes between the cuticle of the hair and that of the root sheath.

The axis of the hair root is always inclined at an angle to the epidermis; it therefore makes with the epidermis an obtuse angle on one side and an acute angle on the other. The arrector pili muscle is always found on the side of the obtuse angle; it therefore, by drawing the hair follicle and its inclosed hair root nearer the perpendicular, causes the erection of the hair. The sebaceous gland is included in the angle between the arrector muscle and the hair follicle. Contraction of the muscle may aid also in the expulsion of the sebum. Extreme contraction of the arrectores pilorum muscles may result from fright, causing the hair to stand on end; in a similar manner cold air may affect, through the pilomotor fibers, the erector muscles of the small hairs distributed over the body and cause the so-called goose flesh

The Epidermal Root Sheath.—The epidermal root sheath consists of an inner and an outer portion, each of which at about the mid-level is divisible into three layers corresponding to the three similar layers of the horny and the mucous portions of the epidermis In those portions of the follicle and in those individual hairs in which the process of cornification is less advanced these subdivisions cannot all be demonstrated, and it is only in the most highly developed hair that they are typically found. This is in accordance with the structure of the epidermis, in which the subdivisions of its horny and mucous portions are typically found only in the more highly developed portions, *e.g.*, the palms and soles.

INNER ROOT SHEATH —The *cuticle* of the inner root sheath consists of thin horny epithelial scales which are imbricated downward, *viz.*, toward the hair bulb, and which interdigitate, in the deeper portion of the follicle, with the similar scales of the hair cuticle. The direction of the imbrication explains the removal of the epidermal root sheath when the hair is forcibly extracted.

The midlayer of the inner root sheath, *layer of Huxley*, one or two cells thick, consists of horny cells which are somewhat flattened, and in which the semblance of a nucleus is sometimes present. It corresponds to the flattened cell layer of the epidermis.
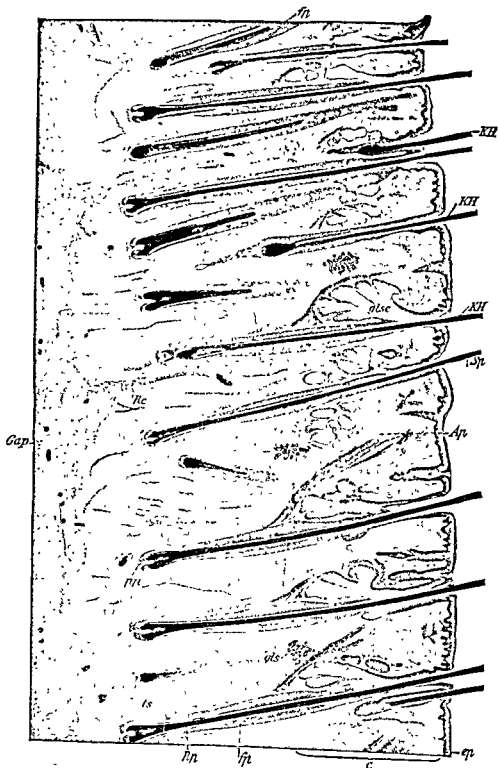
FIG. 284—FROM A SECTION OF THE HUMAN SCALP.

Ap, arrector pili muscle; *c*, corium; *ep*, epidermis; *fP*, epidermal root sheath; *Gap*, muscular aponeurosis, *gls*, sudoriparous gland; *glse*, sebaceous gland; *KH*, so-called "club-hairs" in various stages of molting and regeneration; *pp*, papilla of the hair; *Rc*, fibrous band in the subcutaneous tissue, *Rp*, hair root; *Sp*, hair shaft, *ts*, subcutaneous adipose tissue. Hematoxylin and eosin ×15. (Sobotta)

The outer layer of the inner root sheath, *layer of Henle*, is frequently wanting or imperceptibly blended with the preceding layer. Its cells are clear and highly refractive and their nuclei can but rarely be demonstrated in the usual microscopical preparations. The layer is seldom more than one cell deep. It is homologous with the stratum lucidum of the epidermis.

FIG. 285.—TRANSECTION OF A HAIR NEAR THE MIDDLE OF THE ROOT SHEATH.

a, dermal root sheath; *b*, outer margin of the epidermal root sheath—the light space is the glassy membrane, the polyhedral cells form the outer epidermal root sheath; *c*, Henle's layer of the inner epidermal root sheath; *d*, Huxley's layer; *e*, cuticle of the root sheath; *f*, cuticle of the hair; *g*, cortex of the hair shaft. Highly magnified. (Kölliker.)

OUTER ROOT SHEATH.—The outer root sheath is continuous with the stratum mucosum of the epidermis and therefore contains similar cell types. The granular layer, as in the epidermis, is frequently absent or rudimentary, but can be demonstrated readily in hematein-stained sections of the more highly developed hair follicles. It rests upon a layer, several cells deep, of spheroidal prickle cells. The

outermost layer of the outer root sheath is formed by a basal layer of cylindrical cells. It grows progressively thinner toward the hair bulb, where its cells become mingled with the germinal cells of the hair matrix.

Dermal Root Sheath.—The dermal root sheath presents three layers, an innermost basement membrane or glassy layer, a layer of circular connective tissue fibers and a similar layer of longitudinal fibers. These layers are obviously homologous with the basement membrane, the papillary layer, and the reticular layer of the derma, respectively. The dermal root sheath is, however, entirely devoid of papillae.

The *glassy membrane* is a peculiarly thick homogeneous membrane which is chiefly mesodermal in origin, but whose innermost portion is formed as an exoplasmic product of the adjacent epithelium. This membrane is highly refractive and contains very few connective tissue cells or fibers.

The *circular fibers* of the dermal root sheath contain interlacing bundles of collagenous fibers, which are mostly disposed in a ring-like manner. Elastic fibers are absent. Within this layer is a dense anastomosing plexus of capillary blood vessels, together with a rich subepithelial plexus of unmyelinated nerve fibers.

The *longitudinal fibers* of the connective tissue root sheath also form interlacing fiber bundles, most of which are somewhat obliquely disposed. The bundles are coarser than those of the preceding layer and contain a few elastic fibers. This portion of the root sheath contains many small blood vessels and nerves which supply the plexuses of the circular layer.

The hair follicle in transverse section varies in different races from circular to elliptical form. In the Chinese race the diameter of the follicle and the hair is 100×77 to 85, in the European 100×62 to 72 and in the Negro 100×40 to 60. The more elliptical the form of the follicle the greater the curl of the hair. Curly hair is associated also with follicles having a greater degree of inclination in relation to the skin surface For further details reference should be made to a series of articles on Hair by Danforth.[*]

Atypical Portions of the Hair Follicle.—As already indicated, the hair follicle presents some structural differences at various levels. The typical arrangement is found only in the midportion of the follicle.

In its superficial portion the hair lies free in the follicular lumen, the interval between it and the inner root sheath being only partially occupied by the fatty secretion of the sebaceous gland which enters the lumen of the follicle at the deeper portion of its middle segment. At this level also, the root sheaths of the hair offer a gradual transition from their typical structure to that of the dermal and epidermal layers with which they are continuous.

The hair bulb likewise differs prominently from the typical structure of the hair root. In this portion the germinal layers are very highly developed at the expense of the horny layers. It is, therefore, in this portion that growth is most active. The cells of this region are often deeply pigmented. The increased size of the germinal layer, moreover, produces a distinct bulging of the follicle, which

[*] Danforth, 1925.

incloses the hair papilla and results in the peculiar bulbous shape of the extremity of the hair follicle.

The Hair Papilla.—The structure of the hair papilla is identical with that of the vascular papillae of the derma except that it is constructed upon a much larger scale. It consists of a conical or club-shaped elevation of connective tissue which indents the extremity of the hair bulb. It contains an abundant plexus of capillary blood vessels and a rich supply of unmyelinated nerves. It also contains a relatively large proportion of connective tissue cells.

Regeneration of the Hair.—Hairs are being continuously shed and regenerated, the average life of a hair of the scalp being stated as sixteen hundred days (Stöhr). The shedding of a hair is first heralded by an atrophy of its papilla and *a cornification of its bulb. Growth ceases, and the hair, firmly adherent to its root sheath, is gradually carried,* by the continued growth of the latter, nearer and nearer the surface of the skin.

Its excursion leaves behind a narrowed cell column which still unites the hair with its former papilla.

From this rudiment a new hair germ may form (Unna), a new papilla develop, and the resulting hair grow toward the surface in the path of the molting hair, its eruption being preceded by the falling of its predecessor. The formation of the new hair germ very probably occurs at a point nearly corresponding with the insertion of the arrector pili muscle, where there is a swelling of the root sheath which has been already mentioned as the *matrix* of the hair follicle. This matrix appears very early in the development of the hair, but remains quiescent until regeneration becomes necessary, when the cells are said to proliferate and grow downward filling the space between the atrophic hair and the new bulb.

In infancy and youth shed hairs are also compensated for by new formation from hair germs appearing at the germinal border of the epidermis, the process proceeding in the manner already described for the development of the hair.

THE SEBACEOUS GLANDS

These are branched saccular glands which may be subdivided into two classes, those whose ducts open into the hair follicles, and those whose ducts open upon the free surface of the epidermis. The former are by far the more numerous; the latter occur in the skin of the face, red margins of the lips, labia minora, glans penis and prepuce, and the tarsal glands of the eyelids. With the above exceptions the distribution of the sebaceous glands is coextensive with that of the hairs. They are therefore absent from the palms of the hands and soles of the feet.

A sebaceous gland consists of a dilated saccular fundus, a constricted neck, and a short and narrow duct. Occasional glands are composed of a single saccule, but more frequently they are compound, the several saccules opening by a single short duct which is lined by flattened cells. In the tarsal glands the secreting saccules are connected with the *long excretory duct by means of a short intercalary duct*. The fatty secretion of the sebaceous glands, sebum, is formed by the direct transformation of the protoplasm of the glandular epithelium.
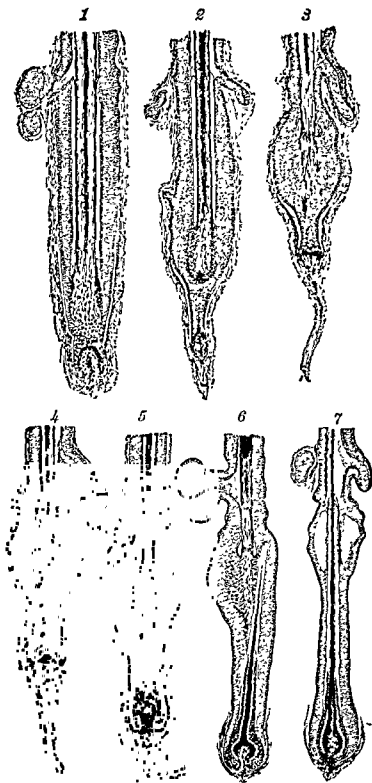
FIG 286—REGENERATION OF A HAIR

Only the follicles and the inclosed portion of the hair shafts are represented. The various stages are numbered in order. (Unna)

The saccules of the sebaceous glands are invested by a thin connective tissue tunic and a delicate basement membrane. They are embedded in the subcutaneous fat or in the deeper part of the corium near the hair follicle. The glands are so disposed as to be included within a triangular space beneath the corium, which is bounded by the arrector pili muscle and the hair follicle. The wall of the saccules comprises several layers of polygonal epithelial cells the outermost of which are cuboidal and rest upon the basement membrane.

In the peripheral layers the lining epithelial cells multiply so actively that the daughter cells are pushed inward until they fill the entire saccule. During this excursion they are progressively farther and farther removed from their source of nutrition, and as they approach

FIG. 287.—*A*, SECTION OF A SEBACEOUS GLAND FROM THE HUMAN SCALP, THROUGH POINT OF OPENING INTO A HAIR FOLLICLE.

Between the basement membrane of the sebaceous alveolus and the hair follicle, the cells exhibit successively later stages of fatty metamorphosis ending in the production of sebum. ×160

B, PORTION OF ALVEOLUS MORE HIGHLY MAGNIFIED. ×550. (Hardesty.)

FIG. 288.—VERTICAL SECTION OF THICK SKIN.

The arterial vessels have been injected with carmine-gelatin. Note capillary supply to papillary layer and to the secretory portion of the sweat glands. (Hardesty.)

the outlet of the saccule, a process of fatty transformation appears within the cell by which its protoplasm becomes changed into a *granulofatty mass* The accumulated product of this transformation and final disintegration of the epithelial cells forms the secretion of the gland. The sebaceous glands are typical *holocrine glands* Continued cell multiplication at the periphery maintains the integrity of the organ. Sebaceous glands of the scalp may become cystic through occlusion of the duct and form wens.

Development.—The sebaceous glands develop as minute epithelial buds from the sides of the hair columns or from the deeper surface of the epidermis These buds soon assume the characteristic flask shape and later become hollowed out

by fatty metamorphosis of their central cells. By this process also their lumen is eventually made continuous with that of the follicle. Secondary saccules of the sebaceous glands are developed in a similar manner by outgrowing germs which appear near the constricted neck portion of the primary saccule.

BLOOD SUPPLY

The larger arteries supplying the skin lie in the subcutaneous tissue. From these vessels branches pass toward the surface, giving off lateral twigs to the rich capillary plexuses in the subcutaneous connective and adipose tissues and about the sweat glands, hair follicles, and sebaceous glands. These arteries continue their course to the deeper part of the corium, where they form an anastomosing

FIG. 289—RECONSTRUCTION OF THE CUTANEOUS BLOOD VESSELS.

a, epidermis, *b*, derma, *c*, subcutaneous tissue; *d*, deep, and *e*, superficial arterial plexus, *f-i*, successive venous plexuses. ×9½. (Spalteholz.)

cutaneous plexus of small vessels Branches from this plexus pass to the papillary layer, where they form a second (subpapillary) plexus from which terminal arteries are distributed to the capillaries of the papillae

The distribution of the veins is similar to that of the arteries. The primary plexus is found in the papillary layer Occasionally a second plexus immediately underlies the first From these plexuses venules pass to the deeper part of the corium, whence after free anastomosis they proceed to the subcutaneous tissue, collecting on the way the venules returning from the hair follicles and secreting glands, and from the subcutaneous connective tissue. The very rich capillary network in the papilla of the hair bulb is worthy of special mention.

The skin over the ventral surface of the hand and foot contains peculiar arteriovenous anastomoses in the form of a glomus of the so-called Sucquet-Hoyer

The saccules of the sebaceous glands are invested by a thin connective tunic and a delicate basement membrane. They are embedded in the subcu fat or in the deeper part of the corium near the hair follicle. The glands disposed as to be included within a triangular space beneath the corium, w bounded by the arrector pili muscle and the hair follicle. The wall of the s comprises *several layers of polygonal ep* cells the outermost of which are cuboid rest upon the basement membrane.

In the peripheral layers the lining ep cells multiply so actively that the daught are pushed inward until they fill the saccule. During this excursion they ar gressively farther and farther removed their source of nutrition, and as they ap

FIG 287.—*A*, SECTION OF A SEBACEOUS GLAND FROM THE HUMAN SCALP, THROUGH POINT OF OPENING INTO A HAIR FOLLICLE.

Between the basement membrane of the sebaceous alveolus and the hair follicle, the cells exhibit successively later stages of fatty metamorphosis ending in the production of sebum ×160

B, PORTION OF ALVEOLUS MORE HIGHLY MAGNIFIED. ×550. (Hardesty.)
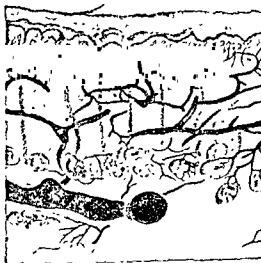
FIG 288—VERTICAL SECTION OF THICK S

The arterial vessels have been injected carmine-gelatin. Note capillary supply to pa lary layer and to the secretory portion of sweat glands (Hardesty.)

the outlet of the saccule, a process of fatty transformation appears with cell by which its protoplasm becomes changed into a granulofatty mass. The ac lated product of this transformation and final disintegration of the epithelia forms the secretion of the gland. The sebaceous glands are typical *holocrine g* Continued cell multiplication at the periphery maintains the integrity of the Sebaceous glands of the scalp may become cystic through occlusion of the du form wens.

Development.—The sebaceous glands develop as minute epithelial buds the sides of the hair columns or from the deeper surface of the epidermis. buds soon assume the characteristic flask shape and later become hollowe

by fatty metamorphosis of their central cells. By this process also their lumen is eventually made continuous with that of the follicle. Secondary saccules of the sebaceous glands are developed in a similar manner by outgrowing germs which appear near the constricted neck portion of the primary saccule.

BLOOD SUPPLY

The larger arteries supplying the skin lie in the subcutaneous tissue. From these vessels branches pass toward the surface, giving off lateral twigs to the rich capillary plexuses in the subcutaneous connective and adipose tissues and about the sweat glands, hair follicles, and sebaceous glands. These arteries continue their course to the deeper part of the corium, where they form an anastomosing

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In the peripheral layers the lining epithelial cells multiply so actively that the daughter cells are pushed inward until they fill the entire saccule. During this excursion they are progressively farther and farther removed from their source of nutrition, and as they approach

Fig. 287.—A, Section of a Sebaceous Gland from the Human Scalp, through Point of Opening into a Hair Follicle.

Between the basement membrane of the sebaceous alveolus and the hair follicle, the cells exhibit successively later stages of fatty metamorphosis ending in the production of sebum. ×160

B, Portion of Alveolus More Highly Magnified ×550. (Hardesty)

Fig 288.—Vertical Section of Thick Skin.

The arterial vessels have been injected with carmine-gelatin. Note capillary supply to papillary layer and to the secretory portion of the sweat glands. (Hardesty.)

the outlet of the saccule, a process of fatty transformation appears within the cell by which its protoplasm becomes changed into a granulofatty mass. The accumulated product of this transformation and final disintegration of the epithelial cells forms the secretion of the gland. The sebaceous glands are typical *holocrine glands* Continued cell multiplication at the periphery maintains the integrity of the organ Sebaceous glands of the scalp may become cystic through occlusion of the duct and form wens.

Development.—The sebaceous glands develop as minute epithelial buds from the sides of the hair columns or from the deeper surface of the epidermis These buds soon assume the characteristic flask shape and later become hollowed out

corium, which collects the lymph from the tissue spaces of both derma and epidermis. The vessels of this plexus communicate with a subcutaneous lymphatic plexus of larger vessels which follow the course of the blood vessels on their way to reach the neighboring groups of superficial lymph nodes.

NERVE SUPPLY

The skin is abundantly supplied with large nerve trunks, both sympathetic and cerebrospinal (sensory). These find their way along the subcutaneous fat and send branches directly to the larger blood vessels, the hair follicles, the sebaceous and sudoriparous glands, to the corpuscles of Pacini, Ruffini, and Golgi-Mazzoni, and to the end-bulbs of Krause, which lie in the connective tissue.

In the cutis vera the nerve trunks form a plexus of delicate fiber bundles in the reticular layer, with a secondary, more closely meshed plexus of finer nerve bundles in the papillary layer. From these plexuses fibrils are distributed to the smaller blood vessels and to the papillae, where many end in tactile corpuscles. Other fibrils penetrate the epidermis, terminating as naked fibrils or as menisci on tactile cells.

In the region of the hair follicle small branches form a network of fibrils in the dermal root sheath. Branches (pilomotor nerves) are also distributed to the arrectores pilorum muscles.

In the sudoriparous glands the nerves form a fine plexus about the membrana propria (epilamellar plexus), from which naked axis cylinders penetrate the basement membrane and terminate between the secreting cells.

type. Such glomi are located in the stratum reticulare and are constantly present in the tips of the digits and in the palmar surfaces of phalanges 1, 2 and 3 and the thenar and hypothenar eminences of the hand. In the foot the glomi occur in comparable regions. They occur also in the nail bed. They are absent during intra-uterine life; they are formed shortly after birth, decrease in number with age and undergo atrophy with advancing senility. The digital glomus as described by Popoff[10] is a normal anatomic unit of specific structure (Fig. 290) consisting of: (1) an afferent artery; (2) a Sucquet-Hoyer canal, or arteriovenous anastomo-
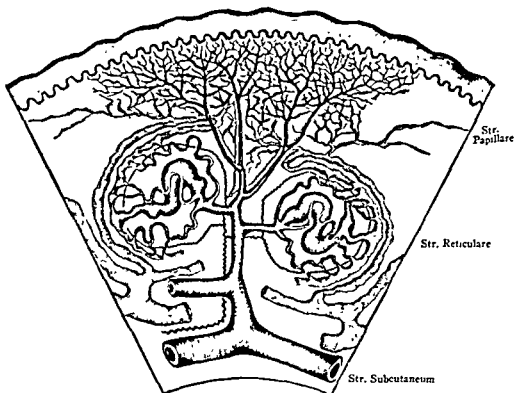
FIG 290—DIAGRAM OF THE VASCULAR ARRANGEMENT OF DIGITAL GLOMUS, SHOWING THE AFFERENT ARTERY, THE COILED SUCQUET-HOYER CANAL, THE AFFERENT PART OF THE CANAL ENTERING THE PRIMARY COLLECTING VEIN (ARTERIOVENOUS ANASTOMOSIS), AND THE SYSTEM OF PREGLOMIC ARTERIOLES SUPPLYING ALL THE CONSTITUENTS OF THE GLOMUS. (Popoff.)

sis proper, characterized by a stout muscular wall; (3) preglomic arterioles, nourishing all the constituents of the glomus; (4) a clear periglomic zone of reticular tissue supplied with abundant unmyelinated nerve fibers which control the function of the S-H canal; (5) a specially arranged system of primary collecting veins; and (6) an outer lamellated collagenous zone surrounding the entire glomus. Popoff ascribes to the digital glomi the functions of control of arteriovenous circulation and the regulation of both the local and general temperature of the body.

The lymphatic vessels of the skin begin as a terminal lymphatic plexus in the

10 Popoff, 1934

frequently compared to the structure of the tubulo-acinose glands. From this point of view the larynx and trachea form the duct stem of the gland, the bronchi form the branching interlobar and interlobular ducts, and the terminal bronchioles (intercalary ducts) end in the numerous acinose air saccules of the lung.

Development.—The original primordium of the respiratory system, beginning with the larynx, is a short linear ventromedial evagination from the cephalic end of the primitive esophagus. This *tracheal groove* becomes separated, distally, thus forming a tube, which grows backward, meanwhile dividing distally into the bronchi which undergo further division to form the successively finer branches of the pulmonary system. The respiratory epithelium is thus of entodermal origin, and becomes enveloped in connective tissue of mesodermal origin.

THE NASAL CAVITY

This cavity is bounded by a cartilaginous and bony wall and is lined with a mucous membrane which, according to the nature of its epithelium, may be divided into three portions: the vestibule, the respiratory portion and the olfactory portion.

Its external and internal openings are the *nares* and *choanae*, respectively. Communicating with the nasal chambers are the sphenoidal, maxillary, frontal, and palatal *accessory sinuses,* and the ethmoidal *air cells.* Their lining membrane is continuous with, and histologically essentially like, though thinner than, that of the respiratory portion of the nostril.

The Vestibule

The vestibule of the nose corresponds very closely to the cartilaginous portion of the nasal wall. Its mucous membrane is continuous anteriorly with the skin and posteriorly with the mucous membrane of the respiratory portion. The vestibule is lined with stratified squamous epithelium, which offers a gradual transition from the moist respiratory epithelium to the dense horny epidermis of the skin. Near its external orifice are numerous coarse stiff hairs, *vibrissae,* connected with which are many sebaceous glands. The vibrissae have no associated arrectores pilorum muscles. Some of the glands also open directly upon the surface of the mucous membrane.

The fibrous lamina propria mucosae of the vestibule is continuous with the corium of the skin, and in it are embedded the deeper portions of the vibrissae and the secreting portions of the sebaceous glands. By its deeper surface the lamina propria is closely attached to the perichondrium of those plates of hyaline cartilage which form the septum and alae of the nose.

The Respiratory Portion

The respiratory portion of the nasal mucous membrane (schneiderian membrane) lines the middle and inferior meatus of the nose. It is continuous anteriorly with the mucous membrane of the vestibule, above with the olfactory mucous membrane, and posteriorly with that of the nasopharynx. The respiratory region

CHAPTER XII

THE RESPIRATORY SYSTEM

The respiratory system may be said to comprise a true respiratory organ, the pulmonary alveoli, in which the interchange of gases between the air and the blood occurs, and a system of duct-like passages leading thereto. This system, beginning with the nasal cavity, successively includes the nasopharynx, larynx,
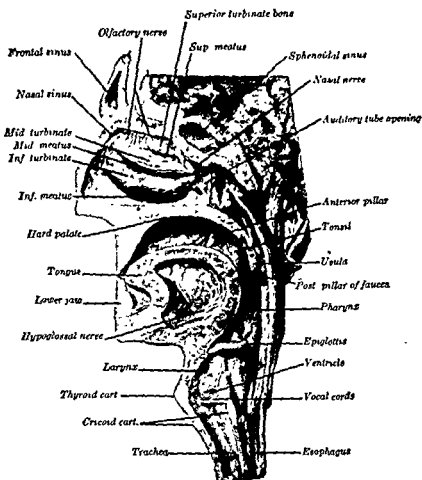
FIG. 291.—PHOTOGRAPH OF AUZOUX MODEL, SHOWING NOSTRIL, PHARYNX, LARYNX AND RELATED STRUCTURES.

trachea, and bronchi of gradually diminishing caliber, and finally ends in the terminal bronchioles leading to the air sacs and pulmonary alveoli.

The arrangement of these several portions of the respiratory system has been

infiltrated with lymphocytes and occasional very minute solitary nodules are found. The lymphatics of the schneiderian membrane lead posteriorly to the lymph nodules of the nasopharynx.
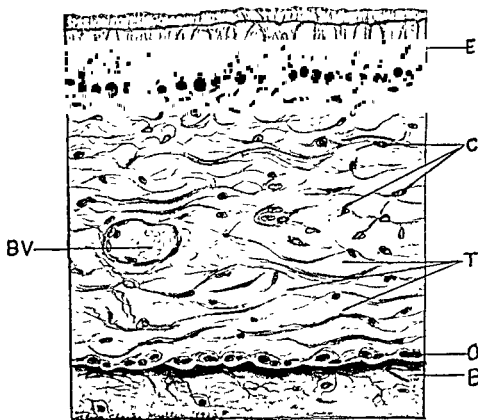
FIG. 293—NORMAL MUCOUS MEMBRANE OF THE ETHMOID CELLS.

E, epithelium, *C*, connective tissue cells; *BV*, blood vessels; *T*, tissue spaces; *O*, osteoblasts; *B*, bone. (From Hajek, *Nasal Accessory Sinuses.*) ×310

THE ORGAN OF JACOBSON

Associated with the respiratory portion is the rudimentary *vomeronasal organ* (of Jacobson) In the embryo of one month it appears as a tubular extension, one on either side, into the corium (lamina propria) of the median septum, opening anteriorly. In transverse section it has a semicircular outline, with its convexity mesial In lower forms, *e g.*, Amphibia, it persists in the adult as a functionally important organ concerned with smell. It is innervated by fibers from the olfactory nerves, vomeronasal nerves, and by the *nervus terminalis*, which is present also in man.[1] In the cat the tall columnar ciliated epithelium (pseudostratified) includes true sensory cells, similar to the olfactory cells. The nervus terminalis contains some myelinated fibers, and may contain both afferent and efferent components (Johnston). In the rabbit it innervates in addition to Jacobson's organ, also a wide area of the nasal septum (Huber and Guild).

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[1] Johnston, 1914.

' is lined with columnar ciliated epithelium of the pseudostratified type, which also contains many mucus-secreting, goblet cells.

The epithelium rests upon a distinct basement membrane which reacts to the specific stains for elastic tissue. The lamina propria consists of a very vascular connective tissue; it varies much in thickness in different portions. It is thinnest in the accessory sinuses and is thickest where it covers the turbinal bones and the adjacent portions of the nasal septum. The lamina propria is richly supplied with both mucous and serous glands. The smaller ones, in the thinner portions of the mucous membrane, are somewhat convoluted; the larger and more numerous are

FIG 292—FROM A SECTION OF THE MUCOUS MEMBRANE OF THE RESPIRATORY REGION OF THE HUMAN NOSE.

a-a, ciliated epithelium; *b-b*, mixed mucoserous glands. ×185.

tubulo-acinose glands. Many of the latter are mixed glands containing both mucous and serous acini. They produce an abundant secretion.

The schneiderian membrane is in all portions extremely vascular, many of its vessels having very thin walls. The thicker portions over the turbinals and the septum are typically *erectile*. The dense connective tissue of these portions is permeated with broad venous channels which are surrounded by circular bands of smooth muscle. Other muscular bundles are longitudinally distributed. The small arteries are contained within the fibromuscular stroma.

The subepithelial portion of the lamina propria contains fine interlacing bundles of connective tissue and many capillary blood vessels. Here and there it is also

and two processes, a distal and a central. Their nuclei are spherical and are disposed in several rows beneath the nuclear zone of the sustentacular cells; thus they form a broad *zone of spherical nuclei*. The distal process (dendron) of the olfactory cell projects as a slender filament whose free end, carrying several fine cilia, reaches the surface of the membrane through a pore-like opening in the cuticular membrane which is formed by the cuticle of adjacent sustentacular cells. The central process (axon) of the olfactory neuron penetrates to the lamina propria and becomes an unmyelinated nerve fiber of one of the many rami of the olfactory

FIG. 295.—OLFACTORY EPITHELIUM OF CALF.

The olfactory cells contrast sharply with the more numerous sustentacular cells. (Hardesty.)

nerve; it passes to the olfactory bulb, where its terminal arborization with the dendrons of the mitral cells forms the olfactory glomeruli.

The *basal cells* are short fusiform or conical cells which form the deepest nuclear zone of the olfactory neuro-epithelial layers. Their cytoplasm is finely granular and their nuclei are ovoid. Frequently they send a short process between the branched ends of the sustentacular cells.

Many small *nerve trunks* occur in the lamina propria. The great majority of these are unmyelinated and are formed by the central processes of the olfactory cells, which processes are true axons. Several of the smaller superficial fiber bundles unite in the deeper part of the lamina propria to form one of the small olfactory nerves. Taken together, about twenty in number on each side, these form two olfactory nerves, unique among cerebrospinal nerves in being collectively unmyelinated. A few myelinated fibers, derived from the trigeminus, are also found in the lamina propria. They distribute their terminal vasomotor branches to the blood vessels, and, by fine sensory filaments which end between the epithelial cells, supply the neuro-epithelial layer. The trigeminus fibers supply a similar innervation to the respiratory mucosa.

THE OLFACTORY PORTION

The olfactory portion of the nasal mucous membrane, the olfactory organ, lines the superior meatus, a portion of the superior turbinate bone and a corresponding portion of the median septum, and its irregular border here and there invades the upper portion of the middle meatus. It consists of a fibrous *lamina propria mucosae* and a clothing of neuro-epithelium. The lamina propria contains elastic as well as collagenous fibers, and many small tubulo-acinose serous glands,

FIG 294—THE OLFACTORY MUCOSA OF A CAT.

a, epithelium, *b*, basement membrane, *c*, lamina propria or corium; *d*, cuticle; *e*, sustentacular cell layer, *f*, olfactory cell layer, *g*, basal cells; *h*, blood vessel; *i*, a tubule of Bowman's glands; *k*, bone Hematein and picrofuchsin Photo. ×270.

the olfactory glands of Bowman Beneath the epithelium is an indistinct basement membrane

The *neuro-epithelium* contains three intermingled cell types, the sustentacular, olfactory, and basal cells.

The *sustentacular cells* are columnar ciliated epithelial cells which possess a distinct cuticular margin. Their nuclei are ovoid, and, since they lie at the same level, they form a continuous superficial *zone of oval nuclei.* The deep ends of the cells are often branched; they interlace with one another and with the processes of the olfactory and basal cells The cytoplasm of the sustentacular cells is finely granular and contains a yellow pigment.

The *olfactory cells* occupy a unique position among neuro-epithelial cells in that they are true nerve or ganglion cells. They possess a small cytoplasmic body

and two processes, a distal and a central. Their nuclei are spherical and are disposed in several rows beneath the nuclear zone of the sustentacular cells; thus they form a broad *zone of spherical nuclei*. The distal process (dendron) of the olfactory cell projects as a slender filament whose free end, carrying several fine cilia, reaches the surface of the membrane through a pore-like opening in the cuticular membrane which is formed by the cuticle of adjacent sustentacular cells. The central process (axon) of the olfactory neuron penetrates to the lamina propria and becomes an unmyelinated nerve fiber of one of the many rami of the olfactory

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The olfactory cells contrast sharply with the more numerous sustentacular cells (Hardesty)

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The *blood vessels* of the olfactory mucous membrane are abundant. Their capillary plexuses form several layers in the lamina propria, and their veins mostly empty, through the ethmoidal veins, into the superior longitudinal sinus—a most significant fact. On the other hand the veins of the respiratory region return their
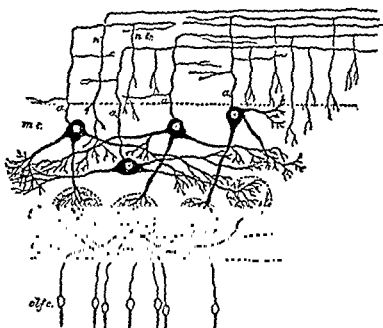
FIG. 296—DIAGRAM OF THE RELATIONS OF THE NEURONS OF THE OLFACTORY NERVE AND OLFACTORY BULB.

olf. c., olfactory nerve cells, located in the olfactory region of the nasal mucosa, whose axons enter the olfactory nerve, *olf n.*, and terminate in relation with the dendrons of the mitral cells, *mc*, in the olfactory glomeruli, *gl* The axons of the mitral cells, *a*, enter the olfactory tract, where they make a sharp bend and pass toward the cerebrum giving off frequent collaterals. At *n'* a nerve fiber appears to end by a free ramification among the mitral cells of the olfactory bulb. (Schafer.)

blood to the internal maxillary vein, while some of those of the vestibule anastomose with the radicles of the facial vein which supply the adjacent skin.

The *lymphatics* of the olfactory region can be readily injected from the subdural spaces of the meninges. They form a network in the connective tissue of the lamina propria

THE NASOPHARYNX

This cavity, like that of the nose, is limited by a bony wall. Its mucous membrane is continuous anteriorly with that of the respiratory portion of the nose, and posteriorly with that of the oropharynx. The structure of its mucous membrane resembles that of the schneiderian membrane, but its dorsal wall, in addition to the ciliated epithelium, the thin-walled blood vessels, and the numerous secreting glands, contains many small nodules of lymphoid tissue These nodules form a considerable mass, the *pharyngeal tonsil.*

The ciliated epithelium of the nasopharynx is also continuous with the lining

epithelium of the auditory (eustachian) tube. The lamina propria is firmly adherent to the bony wall of the dorsal surface, but is more loosely attached laterally and ventrally to the pharyngeal and palatine muscles.

THE LARYNX

The wall of the larynx is formed by several large plates of hyaline cartilage—thyroid, cricoid, and arytenoid cartilages—which are firmly united by ligamentous bands of fibrous tissue The cartilaginous wall incloses a mucous membrane of considerable thickness.

The larger *cartilages* are of the hyaline variety and are prone to ossify in adult life. The tips of the arytenoids, the cornicula of Santorini, the cuneiform cartilages of Wrisberg, and the epiglottis are of the elastic variety of cartilage, and, though frequently much infiltrated with fat, are not, like the hyaline cartilages, subject to ossification The median portion of the thyroid cartilage is also generally elastic in character; this portion does not generally ossify in women. In the lateral hyothyroid ligaments are the minute *triticeous cartilages,* generally hyaline but occasionally fibrous in character.

The intrinsic muscles of the larynx, taking origin from these cartilages, pursue their course beneath the mucous membrane.

The upper portion of the larynx, including the greater part of the epiglottis, as far as the false vocal cords is lined with stratified squamous epithelium which is continuous with that of the pharynx.

The *epithelium* of the vocal cords and that covering the anterior surface of the arytenoids is also of the stratified squamous variety. The re-

FIG 297 —A VERTICAL SECTION THROUGH THE LATERAL WALL OF THE HUMAN LARYNX

a, cartilage ; *b*, laryngeal mucosa, clothed with ciliated epithelium ; *c*, transection of the vocal cord, in this region the mucosa is clothed with stratified squamous epithelium ; *d*, ducts of mucous glands ; *e*, lymphoid nodule ; *f*, muscle ; *g*, mucous glands ; *h*, submucosa ; *i*, blood vessel ; *V*, ventricle of the larynx. Hematein and eosin. Photo. ×8.

maining portions of the larynx, including the base of the epiglottis on its laryngeal surface, the ventricle, and the entire portion below the level of the true vocal cords, are lined with columnar ciliated epithelium of the pseudostratified type. The ciliary motion is directed toward the pharynx. The epithelium rests upon a basement membrane which is less highly developed than in other portions of the respiratory tract.

The *lamina propria mucosae* consists of fibroelastic connective tissue in which are many small tubulo-acinose mucous glands. These are most abundant in the region of the ventricle and the false vocal cords. In this region also there is much diffuse lymphoid tissue, and the lateral and dorsal wall contains several solitary nodules which are so constant in their appearance as to warrant designating them

"laryngeal tonsil" (Fränkel). Occasionally, however, lymph nodules are not present in the mucous membrane of the human larynx. The deeper portion of the lamina propria in certain parts, *e.g.*, in the false vocal cords, contains a few striped muscle fibers in addition to those of the named muscles of the larynx. The false vocal cords and the arytenoepiglottic folds contain loose fibrous tissue and frequently much fat.

The true *vocal cords* are formed of dense bands of elastic and a few collagenous fibers which are covered by a mucosa clothed with stratified squamous
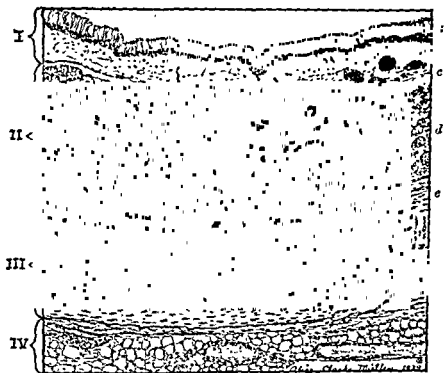
FIG. 298—TRANSECTION OF THE WALL OF A CHILD'S TRACHEA.

I, mucosa; *II*, submucosa; *III*, cartilage; *IV*, outer fibrous coat (*III* and *IV* constitute an adventitia), *a*, columnar ciliated epithelium; *b*, lamina propria; *c*, layer of elastic fibers; *d*, mucous glands; *e*, perichondrium.

epithelium. Their free margin is sharply defined; at their attached margin, however, they blend indistinctly with the lamina propria. The free margin of the vocal cords has no connective tissue papillae on the surface of the lamina propria, but toward the trachea superficial papillae of connective tissue project into the deeper surface of the stratified epithelium.

The mucous membrane of the larynx is freely supplied with blood vessels and lymphatics. The latter terminate in the deep cervical lymph nodes. The nerve fibers, from the recurrent laryngeal, form an abundant plexus in the laryngeal mucosa, from which motor fibers are distributed to the muscles and sensory fibers to the epithelium. The latter end in fine fibrils between the cells of the lining epithelium. In the stratified squamous epithelium, especially that of the epiglottis, small taste buds are also found; none, however, occur on the vocal cords.

THE TRACHEA

The trachea proper extends from the lower border of the cricoid cartilage to the point where it bifurcates into the two primary bronchi, a distance of about four and one-half inches. The wall of the trachea somewhat resembles that of the larynx. It consists of three layers: the mucous membrane, or tunica mucosa; the submucous membrane, or tela submucosa; and the cartilaginous coat, or adventitia.

The *mucous membrane* presents slight longitudinal folds, and is clothed with columnar ciliated epithelium, with numerous goblet cells, which rests upon a delicate basement membrane. The lamina propria mucosae includes a thin inner layer of connective tissue which is richly supplied with small blood vessels and infiltrated by many lymphocytes, and an outer layer of elastic tissue most of whose fibers are longitudinally disposed. The elastic layer begins in the region of the vocal cords in the larynx and is continuous below with the similar layer of the bronchial mucous membrane. Elastic fibers are more numerous in the trachea of the lower mammals than in that of man. A lamina muscularis mucosae, a characteristic structure of the mucosa of the digestive tube, is lacking in the trachea. The elastic membrane occupies the position held by the muscularis mucosae in other organs.

The *submucosa* consists of loose areolar tissue which contains many small tubulo-acinose mucous glands. The ducts of these glands penetrate the mucosa and open upon the free surface of the trachea. They supply an abundant mucous secretion. This coat also contains the larger blood vessels and nerves which are destined for the supply of the mucosa

Fig. 299. — MUCUS-SE-CRETING, TUBULO-AL-VEOLAR GLAND OF THE HUMAN TRACHEAL MUCOSA.

The terminal dark areas are demilunes. Reconstruction. ×200. (Maziarski.)

The *cartilaginous coat* is formed by the C-shaped "ring cartilages" of the trachea (from sixteen to twenty in number) which are firmly united to one another by ligamentous membranes of fibrous tissue continuous with the perichondrium of adjacent cartilage plates. The cartilages are of the hyaline variety and are subject to more or less ossification as age advances. They rarely overlap each other, so that but a single plate of cartilage forms the wall at any given point. Their borders are irregular, and horizontal sections near the upper or lower margin of the cartilage frequently pass through several projections, which, unless properly interpreted, would lead one to infer that the cartilaginous plate was interrupted.

The interval between the ends of the C-shaped cartilage plates is occupied by a membrane of smooth muscle whose transverse fibers unite the adjacent ends of the cartilages. The muscle fibers are inserted into the perichondrium of the cartilages. Many of the fibers are obliquely, and a few of the outermost are longi-

tudinally, disposed. This muscular portion of the tracheal wall forms the so-called *trachealis muscle.* The mucous membrane and submucosa of this portion of the trachea are unusually thick and their mucous glands are exceptionally large. The loose fibrous tissue which invests the outer surface of the cartilaginous coat contains many small sympathetic nerve trunks and ganglia.

THE LUNG

At the root of the lung the trachea divides into a primary bronchus for each lung. By repeated subdivisions—the earliest branches being given off at acute angles, the later ones at more obtuse angles—the smaller bronchi finally end in minute terminal bronchioles which lead through the alveolar ducts to the pulmonary air sacs and alveoli. One may thus distinguish between primary, secondary, and tertiary bronchi, and bronchioles. The mode of division for the main series of bronchi is monopodial, of the smaller bronchi a mixed dichotomy and monopody.[2] According to Piersol the bronchioles are the branches of the fourth or fifth order.

BRONCHI

The wall of the primary bronchi is similar in structure to that of the trachea, but in bronchial tubes which are one or two divisions removed (secondary and tertiary bronchi) from the primary bronchi the plates of cartilage are no longer C-shaped; and a complete lamina muscularis mucosae, internal to the cartilages, forms the outermost boundary of the mucous membrane. In such tubes—typical bronchi—the wall, as in the trachea, comprises: a tunica mucosa, a tela submucosa and a cartilaginous coat, or adventitia.

The *mucosa,* a continuation of that of the trachea, is clothed with tall, columnar, pseudostratified, ciliated epithelium which rests upon a distinct elastic basement membrane. The epithelium is thrown into wavy longitudinal folds. The lamina propria is extremely vascular; it possesses an abundant supply of thin-walled veins of small caliber, together with many lymph vessels. Its connective tissue forms a delicate fibrous reticulum in the meshes of which are many lymphocytes. The outer portion of the lamina propria contains bundles of fine longitudinal elastic fibers, which form a complete layer about the tube. This elastic layer is thickest opposite the ridges and thinnest opposite the troughs of the epithelial waves.

The outer boundary of the mucous membrane contains a well-developed *lamina muscularis mucosae* composed of interlacing bundles of circular smooth muscle fibers. This layer forms a complete muscular coat which is here and there pierced by the ducts of mucous glands whose secreting portions lie in the submucosa.

The *submucosa,* by its broad-meshed areolar tissue, loosely unites the mucous membrane to the cartilage plates. This coat contains the larger blood vessels, nerves, and lymphatics which are distributed to the mucosa. It also contains the

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[2] Miller, 1913.

secreting portions of many tubulo-acinose mucous glands, which occur in groups that in the larger bronchi almost completely surround the tube. The number and size of these glands is in direct proportion to the size of the bronchus. The efferent ducts of the mucous glands penetrate the muscularis mucosae and open upon the free surface in the interval between adjacent folds of the epithelial lining. In the lamina propria mucosae the ducts possess ampullary dilatations which are lined with ciliated cells and contain portions of the mucous secretion.
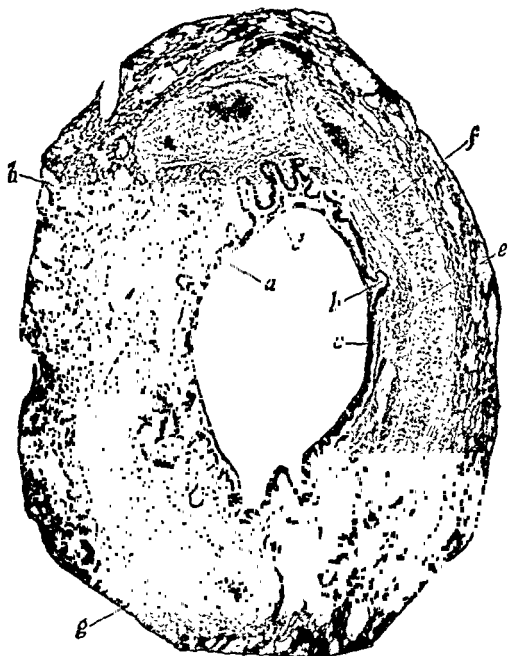
Fig. 300.—A Bronchus from the Human Lung.

a, lining epithelium; *b*, duct of a mucous gland; *c*, lamina muscularis mucosae; *d*, commulated mucus, etc., bathing the surface of the epithelium; *e*, mucous glands; *f*, *h*, *g*, outer fibrous coat; *h*, pulmonary alveoli. Hematein and eosin. Photo. ×34.

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[2] Miller, 1913.

and there divides into the terminal so-called *respiratory bronchioles* (terminal bronchioles).

The *respiratory bronchiole* bears alveoli which become more numerous toward its distal end. It thus contains a variable epithelial lining consisting proximally of a low columnar, sometimes ciliated, epithelium, with distally a more flattened non-ciliated type, and in the alveoli a typical greatly flattened respiratory epithelium including non-nucleated plates. It has a diameter of 0.5 millimeter or less. The epithelium rests upon a thin fibromuscular coat, the continuation of the mucous membrane of the bronchioles. The muscle still forms an almost complete though very thin investment of circular fibers; the muscle fibers, however, are not con-
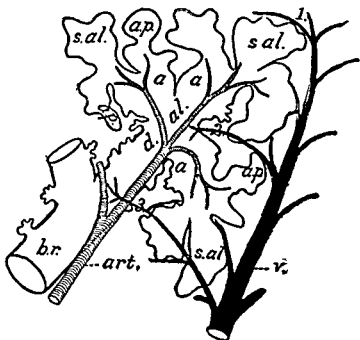
FIG 301 —DIAGRAM OF PRIMARY LOBULE OF LUNG (LUNG UNIT).

b r, respiratory (terminal) bronchiole, *d al*, alveolar duct; *a*, atria, *s al.*, alveolar or air sac; *a p*, pulmonary alveoli, *art*, pulmonary artery; *v.*, pulmonary vein. (Miller.)

tinued into the wall of the pulmonary air sacs. The elastic fibers, derived from the elastic layer of the bronchioles, pass over to the alveolar walls in which they form a delicate network. There are no goblet cells beyond the region of cilia.

The respiratory bronchioles are short branching tubules leading to broader spaces, the *alveolar ducts* (infundibula of Schultze), which are surrounded by air saccules with pulmonary alveoli. According to Miller the alveolar ducts bear numerous alveoli, and are lined with flattened respiratory epithelium, and contain scattered bundles of smooth muscle which end in a delicate sphincter where the duct passes into the nonmuscular *atria*, from three to six for each alveolar duct. Each atrium, of more or less circular outline, opens into a variable number (two to five) of irregular and variable alveolar saccules (air sacs). Each saccule bears on its periphery numerous pulmonary alveoli. The epithelium of the entire bron-

The *cartilaginous coat* is formed by a firm fibrous membrane in which the cartilages are embedded. The plates of hyaline cartilage vary much in number and size, being more or less highly developed in proportion to the size of the bronchial tube. They possess at all times a somewhat crescentic shape. In the larger bronchi three or four cartilage plates with overlapping edges encircle the entire tube. In the lower mammals, *e.g.*, the pig, these overlapping cartilages are so highly developed that the plates often lie three or four deep; in man they are rarely more than one or two deep. As the bronchi diminish in size by division, the cartilage plates are no longer of sufficient size to encircle completely the wall but leave broad intervals in which this coat is only represented by fibrous tissue. In tubes of a diameter of 0.8 to 1 millimeter, *bronchioles*, the cartilages disappear entirely, and in these or somewhat smaller bronchioles the mucous glands are, likewise, no longer found. According to Cutore,[3] the cartilage plates of the intrapulmonary bronchi contain elastic fibers, and are in fact true elastic cartilages.

The outer surface of the cartilages is invested with a clothing of loose fibrous tissue of varying thickness—sometimes known as the *outer fibrous coat*—in which the branches of the pulmonary artery and veins and also many nerve trunks and ganglia are found. In the larger bronchi the two vessels, pulmonary artery and pulmonary vein, are found on opposite sides of the tubes. In the bronchioles only one vessel, the artery, is in relation with the tube, the vein pursuing an independent course within the pulmonary tissue.

Near the root of the lung many small lymph nodes are found in the outer fibrous coat. In the smaller bronchi these are represented by solitary nodules which, it is important to note, are always found in the fibrous connective tissue which forms the outer portion of the bronchial wall. The bronchial lymph nodes and nodules are deeply pigmented, the volume of the pigment being dependent upon the age and occupation of the individual. It is apparently derived by absorption from the surface of the bronchi and is therefore absent in infancy, deficient in youth, abundant in adult life, and especially abundant in those individuals whose occupations have necessitated the inhalation of a dusty atmosphere.

THE BRONCHIOLES

The bronchioles possess neither cartilage, mucous glands, nor lymph nodules. Their epithelium, though still ciliated, is low—short columnar, or, in the smaller bronchioles, cuboidal. The lamina propria mucosae contains many lymphocytes and the elastic tissue forms an almost complete layer of longitudinal elastic fibers.

The muscularis mucosae is relatively more highly developed than in the larger bronchi; it completely encircles the wall and is invested with an adventitious layer of fibrous tissue which contains the small arteries, nerves, lymphatics, a capillary plexus with elongated meshes, and occasional venules.

The fibrous coat (adventitia) of the bronchiole here and there blends with the fibrous bands of interlobular tissue and is in contact with the adjacent pulmonary alveoli. Each bronchiole enters the apex of a *pulmonary lobule* (secondary)

[3] *Cutore, 1914.*

about the alveolar duct that the capillary plexus, in the form of a reticulated membrane of wide capillary vessels, is exposed to the air of two adjacent alveoli, being separated therefrom only by its own endothelium and the epithelial lining of the alveolus.

The lining epithelium of the alveoli, continuous through the alveolar ducts
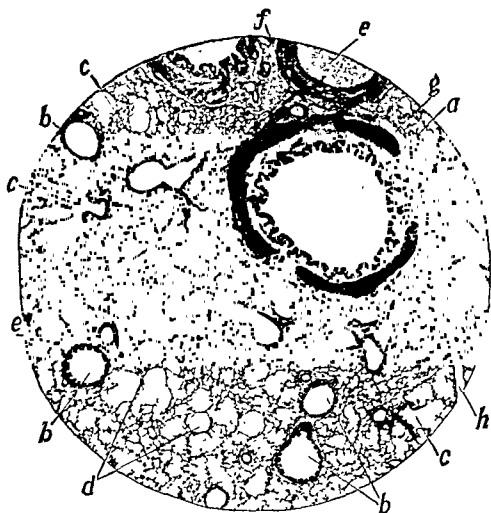
FIG 303—FROM A SECTION OF A CHILD'S LUNG.

a, a small tertiary bronchus, *b*, bronchioles; *c*, bronchioles ending in terminal bronchioles, alveolar ducts etc; *d*. terminal bronchioles in transection, they have a more regular contour and thicker wall than the alveoli, *e*, pulmonary arteries; *f*, a bronchial artery; *g*, a bronchial vein; *h*, interlobular fibrous septum. Hematein and eosin. Photo. ×62.

with that of the respiratory bronchioles, consists of flattened cells and broad protoplasmic non-nucleated plates. These cells are narrower and thicker (cubical) in the prenatal lung and when the lung is collapsed, broader and thinner when it is fully expanded. The completely expanded alveolus in full respiration is two to three times the size of the collapsed or retracted alveolus of full expiration (Kölliker). The elastic fibers of the alveolar wall form a delicate net among the capillaries; in the meshes of this net a few collagenous fibers are found. The normal

chial tree, including the nucleated respiratory cells, contains abundant mitochondria.[4]

Ogawa [5] believes that Miller's term atrium is not necessary in describing the human lung. The alveolar ducts are said to divide two to nine times to reach the air sacs. The mode of division is both dichotomous and monopodial. The air sacs comprise from five to twenty alveoli.
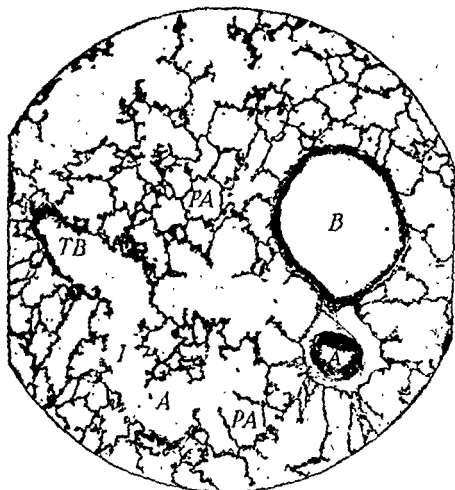
FIG. 302—FROM A SECTION OF A CHILD'S LUNG.

B, bronchiole in transection, with its adjacent pulmonary artery, A; TB, bronchiole, ending in a terminal bronchiole, from which are derived the alveolar duct, I, the atrium, A, and the pulmonary alveoli, P A. In the center of the figure a pulmonary alveolus, P A, is seen in transection; many similar ones are shown Hematein and eosin. Photo. ×105.

THE PULMONARY ALVEOLI

The pulmonary alveoli are minute air chambers, open toward the alveolar ducts, whose extremely thin wall consists of a capillary network, a delicate fibro-elastic reticulum, and a continuous lining epithelium.[6] The alveoli are so densely clustered

4 Meves and Tsukaguchi, 1914.
5 Ogawa, 1920.
6 Bensley, R. D and Bensley, S. H., 1935.

on the basis of a very thorough study of the subject concludes that "the pores are normal constituents of the alveolar walls in the lungs of a wide variety of mammals including man."

<center>THE PLEURA</center>

The pleura is a serous membrane whose visceral layer (pleura pulmonalis) envelops the lung, and whose parietal layer (pleura costalis, diaphragmatis et mediastinalis) lines the thoracic cavity.

The surface of the pleura is clothed with a layer of mesothelium which rests

FIG 305—THE THREE PULMONARY LOBULES CONNECTED WITH A TERMINAL BRONCHIOLE (TB)

The middle lobule is stippled BR, bronchiole; RB, respiratory bronchiole of the first order; TB, respiratory bronchiole of the second order (terminal bronchiole); I, II, III, alveolar ducts; 1, 2, and 3 a, b, c and d, atria, As, alveolar sacs with pulmonary alveoli or air cells. (Adapted from Miller, J. Morphol, 1913, 20:4.)

upon a subserous layer of connective tissue. The mesothelium contains numerous "stomata" which in the costal pleura are only present over the intercostal spaces.

These stomata or pleural pores have been the subject of much discussion. They have been regarded by some as giving direct entrance to lymphatics; but Walters [13]

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[13] Walters, 1913.

respiratory epithelium does not become phagocytic.[7] The area covered by the flat cells of the pulmonary alveoli is equal approximately to 500 square meters (Carrel).

An alveolar duct with its atria, alveolar saccules, blood vessels, lymph vessels and nerves forms a *natural unit of structure*, the *primary pulmonary lobule*.
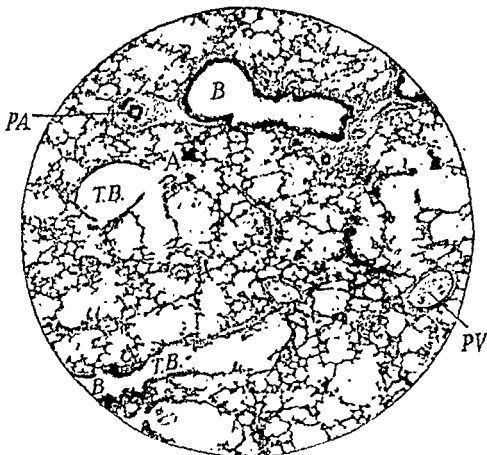
FIG. 304.—FROM A SECTION OF A CHILD'S LUNG.

A, atrium; *B*, bronchioles ending in terminal respiratory bronchioles, *TB*; *PA*, pulmonary artery; *PV*, pulmonary vein Hematein and eosin. Photo. ×50.

Pores leading from one alveolus to another have been described, but Miller[8] denies their presence in the lung of the cat. Ogawa[9] claims that alveolar pores occur normally in the lungs of many mammals. Miller[10] regards these pores as pathologic structures. They are said to occur as secondary ruptures of the alveolar wall in pneumonia. Most recently Macklin[11] has expressed his conviction that these pores ("pulmonic alveolar vents") are "normal openings in the alveolar walls of Mammals, and that they quite probably subserve an important function". Loosli[12]

[7] Miller, 1911.
[8] Miller, 1914
[9] Ogawa, 1920.
[10] Miller, 1925
[11] Macklin, 1935.
[12] Loosli, 1937.

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These stomata or *pleural pores* have been the subject of much discussion. They have been regarded by some as giving direct entrance to lymphatics; but Walters [13]

[13] Walters, 1913

has quite conclusively shown that they are artifacts, an interpretation maintained also by Miller.

The connective tissue contains an abundant network of elastic fibers. It is loosely attached to the chest wall but is more firmly united to the pulmonary tissue. Normally the pleura contains no lymph nodes (Miller). The fibro-elastic stroma of the parietal pleura contains a small amount of smooth muscle.

The pleura contains many small blood vessels, and an abundant plexus of blood and lymphatic capillaries. Its innervation includes both sympathetic and cerebral (vagus) fibers. Both are apparently unmyelinated. The sympathetic nerve fibers are supplied to the walls of the blood vessels; they are vasomotor in function. The vagus fibers are sensory in nature, and terminate in lamellar corpuscles, and as free end fibrils.

THE LOBULE OF THE LUNG

If carefully examined, the surface of the pulmonary pleura presents minute polygonal areas (10 to 25 millimeters in diameter), the bases of the *anatomical*

FIG 306.—TWO ALVEOLI OF A CHILD'S LUNG.

In *A*, the wall is cut across and viewed in profile; *B*, a tangential section showing the cup-shaped bottom of the alveolus and the pulmonary epithelium in surface view; *c*, a pulmonary venule. ×425.

(or secondary) *lobules*, whose borders mark the attachment of fine bands of *interlobular connective tissue*, outlined by pigmented lines. In microscopical preparations still finer bands may be found, which traverse the pulmonary tissue in the direction of the root of the lung, and which partially outline minute conical areas, the true *pulmonary* (or primary) *lobules*, or *lung units*, whose bases are directed toward the pleura, and their apices toward the root of the lung. In many of the lower mammals, *e.g.*, ox, these primary functional lobules are more distinctly outlined by the interlobular connective tissue than is the case in these lobules in man.

At the apex of the secondary lobule a small bronchiole (intralobular bronchiole) enters and divides into its respiratory bronchioles (from 30 to 100). This secondary pulmonary lobule consists of a collection of from 50 to 200 smaller histological units or *primary pulmonary lobules*. At the same point a terminal branch of the pulmonary artery enters with the bronchiole and supplies the anastomosing capillary plexus in the alveolar walls. Branches of the *bronchial artery* do not supply any of the primary intralobular structures, and the pulmonary veins which return the blood from the alveolar capillaries arise at the periphery of the primary lobule and immediately enter the interlobular connective tissue.

The interlobular connective tissue contains the smaller branches of the pulmonary veins, the lymphatics returning from the pleura, and the unmyelinated nerve trunks which are destined for the supply of the pleura and the intralobular pulmonary tissue.

BLOOD SUPPLY OF THE LUNGS

The blood supply of the lungs is derived from two distinct sources, the pulmonary arteries and the bronchial arteries. The former is destined chiefly for aeration in the capillaries of the alveolar walls, the latter for the nutrition of the bronchial walls.

The *pulmonary artery* enters at the hilus in company with the vein and the bronchus. It follows the bronchus throughout its course and supplies an arterial branch to each of its subdivisions. The large arteries nearly equal in size the bronchus in relation to which they lie, but the smaller branches are not more than

FIG 307.—TRANSECTION OF THE PLEURA OF AN INFANT.

a-a, layer of mesothelium; *b,* submesothelial connective tissue; *c,* pulmonary alveoli; *d,* a small blood vessel. Hematein and eosin Photo. ×470.

one-fourth to one-fifth the diameter of their bronchus. Throughout their course the branches of the pulmonary arteries lie *on* the wall of the bronchi, *viz.,* in the outer fibrous coat or attached thereto by a broad band of fibrous tissue. Moreover each bronchus is accompanied by only one branch of the pulmonary artery and receives no capillaries from it.

At the apex of the secondary pulmonary lobule the pulmonary artery enters with the bronchiole It resolves into smaller arterioles corresponding in number approximately to the number of respiratory bronchioles, each of which again breaks into several small twigs—one for each atrium, according to Miller—which supply the capillary networks in the walls of the alveolar ducts and alveoli. The pulmonary capillaries form an exceedingly dense net of anastomosing vessels in the walls of the alveoli, the meshes of the capillary net being frequently, in the deeper portions of the lung, of less diameter than the vessel itself. At the periphery of the lobule the capillaries converge to form several venules which unite to form larger veins in the interlobular tissue. These veins pursue an independent course and are always found at a considerable distance from the bronchioles and lobular branches of the pulmonary artery (see Fig. 301).

The smaller branches of the pulmonary artery near the surface of the lung supply arterial twigs to the adjacent portions of the pleura. From the capillaries of the pleura minute venules enter the interlobular tissue and join the interlobular veins.

The *interlobular veins* (pulmonary veins) follow the fibrous septa toward the hilus. They soon come into relation with the bronchi and are then found on that side of the bronchus opposite the pulmonary artery. The vein, like the artery, lies
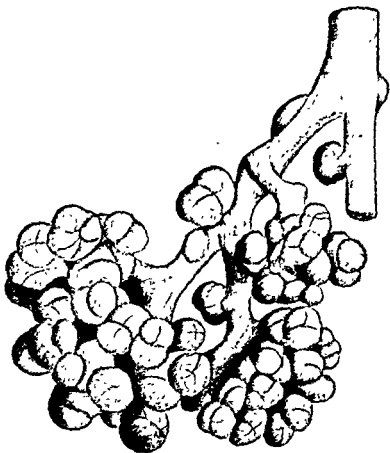
FIG. 308.—WOOD'S METAL CAST OF PORTION OF SECONDARY LOBULE OF HUMAN LUNG, SHOWING DISTAL END OF BRONCHIOLE, A RESPIRATORY BRONCHIOLE, THREE TERMINAL BRONCHIOLES AND SEVERAL ALVEOLAR DUCTS.

The atria are hidden by the spheroidal air sacs on the surface of which appear the bulging pulmonary alveoli (Hardesty)

outside of the bronchial wall in the adjacent fibrous tissue. It is, as a rule, only those bronchi whose wall contains cartilage plates which are in relation with both pulmonary artery and vein; the smaller bronchioles are usually accompanied by the artery only. Those veins which accompany the bronchi receive smaller radicles from the bronchial wall and by union with their fellows form larger and larger vessels which finally make their exit as the pulmonary veins and pass to the left auricle of the heart.

The *bronchial arteries* also follow the bronchial tubes in all their ramifications as far as the primary lobules. The bronchial arteries vary from two to four in number; they arise from the thoracic aorta. The right bronchial artery may arise

from the first right intercostal artery. The larger branches are found in the outer fibrous coat near the cartilages, the smaller ones lie in the submucous and mucous coats.

In contradistinction to the pulmonary vessels the bronchial arteries are found *in* the wall of the bronchi, not outside of the bronchial wall. They supply capillaries to all of the tissues of the bronchi. The bronchial capillaries reunite to form small venules whose course differs with the size of the tube. In the terminal bronchioles
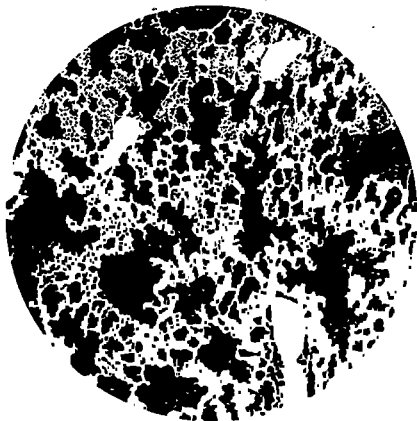
Fig. 309—From the Lung of a Dog Whose Blood Vessels Had Been Injected with a Gelatinous Mass, and Appear Black.

The outlines of the pulmonary alveoli and atria are well shown. Many of the alveoli have been cut tangentially and present a surface view of the capillary network; in others the alveolar wall is cut across and is seen in profile. X125.

these venules pass directly to the interlobular veins, and, according to Miller, the pulmonary veins receive a similar acquisition at each division of the bronchi. In the larger bronchi, however, the venules unite within the bronchial wall to form the radicles of the bronchial vein which, lying in the fibrous tissue of the bronchial walls, retrace the course of the bronchi to the hilus, where they make their exit as the *bronchial veins* and join the azygos vein. Thus, only the walls of the larger bronchial tubes are supplied with bronchial blood, and, according to Schaffer, a few branches at the root of the lung are also distributed to the adjacent pleura.

Many of the bronchioles, the respiratory bronchioles, and also the alveolar ducts, pulmonary alveoli, and the pleura all receive their nutrition from the pulmonary arteries. There are no anastomoses between the pulmonary arteries and veins except among the capillaries of the alveolar walls. The vasa vasorum of the pulmonary artery are supplied by the bronchial arteries.

The studies of Miller [14] reveal that the blood supply of the pleura varies with different animals. "In the lungs which possess a thick pleura and have secondary
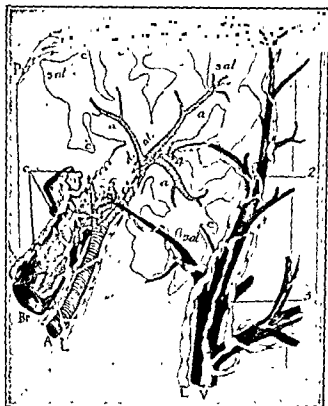
FIG. 310—SCHEME OF A PRIMARY LOBULE WITH ITS BLOOD VESSELS AND LYMPHATICS.

P., pleura, *Br*, bronchiolus respiratorius which divides into two ductuli alveolares (*d al.*), only one of which is carried out in detail; *a a a.*, three atria, each of which has a number of sacculi alveolares (*s al.*) opening into it, around the periphery of which are the alveoli pulmonis, *c*. Alveoli are also connected with the bronchiolus respiratorius, ductulus alveolaris and the atria. *A.*, pulmonary artery which divides into three atrial branches and each atrial branch divides into branches which are distributed to the sacculi alveolares, these latter branches give origin to the capillary network in the walls of the air spaces *L.*, lymphatics; *V.*, pulmonary vein and its branches of origin; *1, 2, 3, 4, 5*, regions of origin of perivenous lymphatics. The bronchial artery does not extend as far as the primary lobule; for the nerves, see Fig. 311   (Miller.)

lobules marked off by pronounced septa as in the lung of the ox, the sheep and man, the bronchial artery extends to the pleura and furnishes a special blood supply to the walls of the lymphatics. In those lungs which have a thin pleura as the lung of the cat, the dog and the rabbit, it is the pulmonary artery which supplies the pleura with blood." .

[14] Miller, 1917.

LYMPHATICS

The pulmonary lymphatics include peribronchial, periarterial, perivenous and pleural systems. They form a plexus in the walls of the bronchi and bronchioles, penetrating into the mucous membrane. Branches from this plexus frequently anastomose with perivascular lymphatic vessels about the branches of the pulmonary artery and veins. A close network of lymphatic vessels is also found in the pleura, its efferent vessels passing into the interlobular tissue to join those vessels which accompany the veins. The pulmonary lymphatics are supplied with frequent valves and numerous anastomoses. At the atria the lymphatics pass to the interlobular septa so that the alveolar walls lack lymph vessels (Fig. 310).

The lymphatic vessels of the bronchi are connected with larger lymphatic vessels of the outer fibrous coat and with the lymph nodules in the walls of the larger tubes. Many of the larger vessels in the outer fibrous coat of the bronchi, and also those which accompany the pulmonary artery, enter those lymph nodes which are in relation with the bronchial walls at the root of the lungs. The pleural lymphatic plexus and the vessels accompanying the pulmonary veins, after pursuing much of their course through the interlobular connective tissue in company with the pulmonary veins, also open into the bronchial lymph nodes. Much pigment is conveyed through these vessels and is deposited in (a) the interlobular connective tissue, (b) the fibrous tissue about the pulmonary arteries, and most abundantly in (c) the bronchial lymph nodules and nodes.

In the lymphatics of the bronchi, arteries, most venous trunks and the greater part of the pleura, the flow of the lymph is toward the hilus of the lung. In the lymphatics about the veins, the flow in those vessels which are situated just beneath the pleura and communicate with the pleural rete of lymphatics may be *toward the pleura*. According to Miller [15] this probably explains why tubercles may be found in the pleura while none may be present in the deeper part of the lung.

Lymphoid tissue forms an important constituent of the lungs, serving as filters in the lymph circulation and as centers to which the phagocytes carry their collected material. It occurs as nodes, nodules, or as smaller masses of more diffuse lymphoid tissue; it may be peribronchial, periarterial, perivenous or subpleural in position.
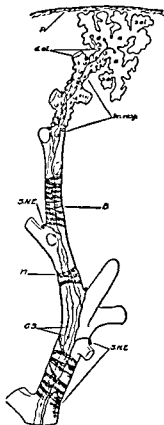
FIG 311.—THE BRON-
CHIOLI AND THE AIR
SPACES AND THE
NERVES.

P., pleura; *s al,*
sacculi alveolares, *a.,*
atria, *d.al,* ductuli
alveolares; *br. resp,*
bronchioli respiratorii,
B, bronchiolus *G S,*
ganglion cells; *M,*
postganglionic fiber
ending in smooth mus-
cle, *S N.E,* afferent
nerve ending. (Bron-
chioli and air spaces
after Miller; nerves
after Larsell, *J. Comp.
Neurol,* 1922, 35:97.)

[15] Miller, 1917

Lymph nodes are associated with the larger divisions of the bronchi and located at the points of branching. The smaller masses are found in greatest numbers at the periphery of the primary and secondary lobules.[16]

The lymph nodules and lymphoid tissue found along the bronchi in the human lung are generally said to receive their blood supply from the bronchial arteries. In the rabbit, however, Miller [17] finds that these masses of lymphoid tissue do not receive their blood supply from the bronchial arteries but from the pulmonary artery. Reference should be made to the book on The Lung by William Snow Miller (Charles C. Thomas, Springfield, Ill., 1937).

NERVE SUPPLY

The nerves of the lungs are derived from the anterior and posterior pulmonary plexuses of the sympathetic system. They are distributed to the wall of the blood vessels, where they form a delicate plexus with terminal fibrils among the smooth muscle fibers, and to the walls of the bronchial tubes. Small nerve trunks, with which many minute ganglia are connected, occur in large numbers in the outer fibrous coat of the bronchi.

From these nerve trunks and ganglia fibrils are distributed to the bronchial mucous membrane, in which they supply the muscularis mucosae, and form a terminal plexus beneath the epithelial coat. These fibers have been traced to the respiratory bronchioles, where they are said to form a delicate plexus within the lobule in the interalveolar walls.[18] Sensory fibrils are supplied by the vagus nerve. The vagus contributes to the bronchi and their subdivisions also motor fibers, for the most part probably indirectly through the sympathetic ganglia.

MEGAKARYOCYTES AND MAST CELLS

Howell and Donahue [19] present evidence, from studies chiefly of the cat, suggesting that the lung is an important accessory source of platelet production. Comparative counts of platelets in companion arteries and veins showed with few exceptions that arterial blood contains a larger number of platelets than venous blood. A typical example from their protocols is as follows: Carotid artery, 11,220,000 red blood corpuscles, 333,000 platelets, ratio 1:33.6; jugular vein. 10,260,000 red blood corpuscles 316,000 platelets, ratio 1:32.1. Among a total of forty-four observations, thirty-four gave a higher count of platelets in the artery than in the vein, eight gave an equal count, two showed a higher count in the vein. Histological preparations of the lung of the cat contained many cells interpreted as megakaryocytes with pseudopods fragmenting into platelets. In some normal cases as many as 40 "megakaryocytes" appeared in an area of 100 sq mm. Under experimental conditions the number of giant cells in the lung might be at least four times as great. They conclude that "in extrauterine life giant cells are concentrated in the marrow and the lungs, with the maximum of their activity in platelet production in the lungs." They consider the lungs rather than the marrow as the chief source of platelets.

It may be emphasized, however, that the difference in the number of platelets in

16 Miller, 1911.
17 Miller, 1917.
18 Wolff, 19
19 Howell, 1

arterial and venous blood was generally small; the difference in the ratio of platelets to red blood corpuscles in artery and companion vein was in the majority of samples so small as to seem without significance Furthermore, the difference in the number of platelets in arterial and venous blood might be the result of a difference in the degree of pressure; in the more slowly moving venous blood as compared with relatively more rapidly flowing arterial blood the relatively adhesive platelets would tend to cohere in larger numbers on the vessel wall when samples of blood are withdrawn for examination. One must also consider the possibility that larger platelets of venous blood may fragment into smaller platelets in passing through the capillary mesh of the lungs; it is well known that the venous sinuses of the red marrow contain a relatively large number of larger platelets.

As regards histological preparations of the lung, it must be stated that while megakaryocytes with typical "basket" nucleus are clearly recognizable in routine preparations of marrow, fetal liver, lymph nodes and the spleen, such cells are only rarely to be seen in the normal lung Typical megakaryocytes may appear in the blood and the lungs in certain leukemias. Naked and degenerate megakaryocyte nuclei, sometimes in considerable numbers, can readily be seen in the alveolar capillaries in many routine preparations of normal lungs. The possibility remains that such nuclei, having temporarily stenosed a capillary and thus giving opportunity for platelets of various sizes to collect and cohere, might simulate giant cells in the process of platelet production.

Many of the apparently naked megakaryocyte nuclei have persistent fragments of the original granular cytoplasm. Such cytoplasmic projections provide favorable surfaces for the adhesion of circulating platelets. Moreover, since megakaryocyte nuclei with portions of the original cytosome may enter the blood stream from the venous sinuses of the bone marrow, it is quite possible that relatively normal megakaryocytes also may occasionally secure admission to the prepulmonary circulation. In sections of the lungs of the cat, megakaryocyte nuclei with variable amounts of granular cytoplasm occurred in each of the several subdivisions of the pulmonary artery as well as in the alveolar capillaries. An example of an apparently normal megakaryocyte with several long granular pseudopods could be demonstrated in the pulmonary artery accompanying a tertiary bronchus.

It seems clear that the megakaryocytes of the lung originate in the bone marrow. The first capillary mesh encountered is in the lung. The lung serves as a filter for circulating megakaryocytes, naked giant-cell nuclei and giant platelets which may have entered the venous sinuses of the marrow. The lung is not properly considered an organ of origin of megakaryocytes. While the megakaryocyte nuclei of the lung with persistent portions of the original granular cytoplasm may contribute a modicum of platelets, the total histologic evidence, including especially that of the presence of occasional megakaryocytes and naked nuclei in the pulmonary arteries, renders dubious the claim that the lung is normally a seat of megakaryocyte origin and an important organ of platelet production.

The lung contains also large numbers of mast cells. These are especially abundant in the peribronchial, perivascular and the subpleural regions. The mast cells may have long processes These are filled with fine granules which take a reddish purple color with Wright's stain. The processes may extend into the smaller blood vessels and segment into plastids very similar to blood platelets. If the mast cells function as producers of heparin, as claimed by Holmgren and Wilander,[20] then the richness of the lung in these cells would explain its high content of heparin.

[20] Holmgren, H and O Wilander, 1937

CHAPTER XIII

THE DIGESTIVE SYSTEM

The digestive system includes the cavities of the mouth, pharynx, esophagus, stomach and intestines, together with the accessory glands—the salivary glands, pancreas and liver. Associated with the mouth and coöperating in the function of the essential organs of digestion are also the teeth and the tongue.

THE MOUTH

The walls of the oral cavity comprise a mucous membrane, a submucous layer of connective tissue, and a muscular or bony paries.

Mucous Membrane.—The mucous membrane (mucosa) is clothed with a layer of stratified squamous epithelium which presents, at the margin of the lips, a gradual transition to the epidermis of the skin, and at the fauces is continuous with the lining epithelium of the faucial isthmus and the pharynx. The epithelium rests upon a distinct basement membrane (*membrana propria*).

Lamina Propria.—The lamina propria (corium, stratum proprium) upon which the epithelium rests, consists of dense areolar tissue, the superficial portion of which specially abounds in elastic fibers. This portion of the corium consists of rather delicate connective tissue bundles which at frequent intervals are prolonged into the epithelial coat in the form of minute conical papillae, similar to those of the skin, whose height varies with the location. The tallest papillae are found on the gums and at the margins of the lips, the lowest on the inner surface of the cheeks and the soft palate.

The papillary layer of the corium contains a plexus of capillary blood vessels which is connected with a network of small arteries and veins in the deeper part of the lamina propria

Submucosa.—The submucosa consists of looser connective tissue which blends insensibly with that of the mucosa, and unites the mucous membrane to the subjacent muscles and bones forming the wall of the oral cavity. In most portions the buccal mucous membrane is but loosely connected with the underlying parts, but in the hard palate and the gums this union is very firm.

Lymphoid Tissue.—Lymphoid tissue occurs in considerable abundance in the oral mucous membrane. Areas of diffuse lymphoid tissue are of frequent occurrence and small lymph nodules are occasionally found. The lymphatic vessels form a plexus in the lamina propria, which empties into the larger vessels in the submucosa.

Secreting Glands.—Secreting glands occur in considerable abundance in all portions of the buccal mucous membrane except that covering the gums. The glands are of the tubulo-acinose type and produce either a pure mucous secretion or, in the case of the larger ones, a mixed mucous and serous secretion. The ducts of the glands are lined with columnar cells which, near the mouth of the duct, offer a gradual transition to the stratified squamous epithelium of the mucosa. The glandular epithelial cells of the secreting portions become swollen and
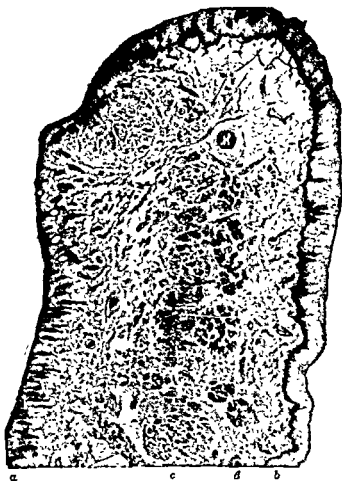
FIG 312—FROM A SECTION THROUGH THE LIP OF AN INFANT.

a, cutaneous surface; *b*, epithelium of the oral mucosa; *c*, layer of striated muscle; *d*, layer of mucous glands Photo ×10.

clear *after* a period of rest, but are shrunken and present a faint cytoplasmic reticulum *after activity*. The different glands of the same region, and even different cells in the same gland, often exhibit various stages of secretory activity. The fundus of the secreting glands frequently extends into the loose connective tissue of the submucosa At the margin of the lips and more rarely in the neighboring portions of the buccal mucous membrane are small sebaceous glands which open directly upon the free surface. The oral glands will be further described below under salivary glands.

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The slightly constricted border between the root and the crown, which is surrounded by the soft tissues of the gum, is known as the *neck* of the tooth.

The tooth consists of a superficial calcareous portion and a central medulla, the *dental* or *pulp cavity*, which occupies the axis of the tooth and which contains a peculiar embryonal type of connective tissue, very similar to reticular tissue, the *dental pulp*. At the tip of each fang is an opening, the *foramen apicis dentis*, leading to a narrow canal which penetrates the wall of the tooth and permits the entrance of the nerves and blood vessels which supply the pulp.

The calcareous wall of the tooth is formed by three distinct tissues: *dentin* or *ivory, enamel* and *cementum*. The dentin incloses the entire pulp cavity and is in turn covered by the enamel and cementum, the enamel forming the superficial layer of the crown, the cementum that of the root of the tooth.

Dental Pulp.—The dental pulp is an embryonal type of connective tissue which is rich in branching stellate cells and poor in fibers. It contains no elastic fibrils, and the delicate collagenous fibers instead of forming bundles are arranged in an interlacing network, the fine fibrils of which are in intimate relation with the connective tissue cells. It accordingly closely resembles reticular connective tissue. The stellate connective tissue cells are scattered throughout the entire pulp, but at the periphery of the cavity are closely crowded and are much enlarged. These peripheral cells form a layer of *odontoblasts* which is in contact with the dentin.

The odontoblasts are cylindrical branched connective tissue cells whose long axis (about 40 μ) is perpendicular to the surface of the adjacent dentin. From their apex a delicate process is sent into the dentinal canals, in which they frequently extend all the way through the dentin. Lateral processes from the cell bodies of the odontoblasts interlace with each other and firmly unite the cells into

FIG 314—AN AXIAL GROUND SECTION OF TOOTH, SHOWING THE SEVERAL STRIPES OF THE DENTIN AND THE ENAMEL

Enamel

Contour lines of Retzius

{ *Prism stripes of Schreger*

{ *Contour lines of Owen*

Dentinal tubules

{ *Granular layer of Tomes*

{ *Incremental lines of Schreger*

Cementum

Pulp Cavity

Root canal

a membranous layer. Other processes are given off from the base of these cells and intermingle with the fibers of the pulp, so that if this tissue is forcibly separated from the dentin the odontoblasts remain adherent to the connective tissue of the pulp The nuclei of the odontoblasts are found near their inner or basal extremity. Their cytoplasm is of considerable extent as compared with that of the other connective tissue cells of the pulp.

The dental pulp is richly supplied with blood vessels, derived from a nutrient artery which enters through the root canal, its several branches forming a net-

FIG. 313.—AXIAL SECTION OF A HUMAN MOLAR TOOTH.
C, cementum; D, dentin; P, pulp cavity; S, enamel. ×8. (Sobotta.)

THE TEETH

STRUCTURE

Each tooth rests in a bony socket in the alveolar process of the maxillary bone, and is also held in place by the periosteum of the alveolar sac and the adjacent portion of the gum. The tooth is divisible into a free portion or *crown*, and a concealed portion or *root* which usually consists of from one to three *fangs*.

The slightly constricted border between the root and the crown, which is surrounded by the soft tissues of the gum, is known as the *neck* of the tooth.

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Fig. 314—An Axial Ground Section of Tooth, Showing the Several Stripes of the Dentin and the Enamel.

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The dental pulp is richly supplied with blood vessels, derived from a nutrient artery which enters through the root canal, its several branches forming a net-

work of minute arterioles and capillary vessels in the center of the pulp cavity, and a peripheral close-meshed capillary network which is in close relation with the layer of odontoblasts. Numerous delicate lymphatic vessels, uniting to leave

FIG. 315.—FROM A LONGITUDINAL SECTION OF THE NECK OF A CHILD'S TOOTH AND THE ADJACENT ALVEOLUS.

a, enamel; b, cementum; c, dentin; d, bone; e, periosteum; f, corium; g, lymphoid tissue; h, stratified squamous epithelium of the gum; i, circular dental ligament; k, epithelial remnants; l, blood vessels. ×25. (Kölliker.)

the root as one or several large vessels, have been demonstrated in the tissue of the dental pulp.[1]

A rich nerve supply is derived from fine branches which also enter by the root canal. Most of the nerve fibers lose their myelin sheaths soon after they enter the pulp. They form a primary plexus in the connective tissue from which fine

[1] Schweitzer, 1907.

fibers pass to the periphery and form a marginal plexus beneath the odontoblasts. From here delicate terminal sensory fibrils ramify over the odontoblasts and pass in great abundance into the dentinal tubules, usually two to each tubule.[2] This peripheral distribution of nerve fibrils explains the extreme sensitiveness of the dentin. Sympathetic fibers supply the muscle cells of the pulp arterioles.

Dentin.—The dentin surrounds the entire pulp cavity except at the opening of the root canal. It is a fine calcareous substance which resembles bone in that it consists of a collagenous fibrous matrix and is infiltrated with lime salts. The matrix is a fine fibrous network of dense connective tissue, the majority of whose fibers are disposed in a longitudinal direction. The meshes of the matrix are almost completely filled by a deposit of calcareous salts which gives the dentin its bony
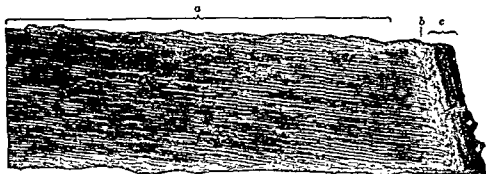
FIG. 316—FROM A SECTION OF A HUMAN TOOTH WHICH HAD BEEN GROUND TO EXTREME THINNESS.

a, dentin; *b*, granular layer of Tomes; *c*, enamel. Photo. ×150.

consistence. Dentin consists of about 28 per cent organic and 72 per cent earthy matter. The latter includes calcium phosphate, about 67 per cent; calcium carbonate, about 3 per cent; and magnesium phosphate, with a trace of calcium fluoride.

Here and there, especially toward its peripheral border and near the apex of the tooth, the dentinal matrix fails to become calcified. Such uncalcified areas, *interglobular spaces*, are encroached upon by the rounded or globular margins of the adjacent calcified matrix which forms the so-called *dentinal globules*.

The dentin is everywhere permeated by a system of canaliculi, the *dentinal tubules* or *canals*, which extend in a radial manner from the pulp cavity outward to the cementum and enamel. Their course is characteristically curved, resembling the letter *s*. The cavity of the dentinal tubules is partially occupied by the dentinal processes (fibers) of the odontoblasts, an arrangement which may be compared to that existing between the processes of the bone cells and the canaliculi of bone. At their inner extremity the dentinal tubules are 2 to 4 μ in diameter, but they taper very gradually, especially in the outer portion of their course, where they finally reach a diameter of no more than 0.5 to 1 μ.

[2] Mummery, 1912

The dentinal tubules may divide dichotomously in the inner third of their course; beyond this point they give off very fine lateral twigs, which at first leave the parent tubule nearly at right angles, but later are slightly inclined outward.

At their distal end most of the dentinal tubules divide into a group of terminal branches, some of the arborizations being very extensive, others consisting of but two or three subdivisions. The coarser branches are frequently looped, the distal end of the loop often anastomosing with adjacent tubules. In their course through the dentin those canaliculi which enter the larger interglobular spaces are continued through these spaces without interruption. The walls of the dentinal tubules are formed by extremely dense calcareous *dentinal sheaths* (of Neumann) which are very resistant to the action of acids.

The curvatures in the course of the dentinal tubules are of two types: the longer primary curves and the shorter spiral secondary curves. They occur with extreme regularity and as a result give rise to certain parallel lines in the substance of the dentin which

FIG. 317.—SECTION OF FANG PARALLEL TO THE DENTINAL TUBULES, HUMAN CANINE (WALDEYER.)

1, cementum, with large lacunae, canaliculi and indications of lamellae; *2,* granular layer of Tomes with large interglobular spaces, *3,* dentinal tubules. ×300. (From Quain, *Anatomy*)

FIG. 318—DENTIN FROM A GROUND SECTION OF A HUMAN MOLAR, SHOWING THE DENTINAL TUBULES CUT ACROSS.

The tubules appear as dark round or oval areas in the dentinal matrix Each tubule is surrounded by a narrow lighter halo, corresponding to the sheath of the tubule, perhaps an optical effect. ×750.

follow the contour of the dentinal surface. These are known as the *incremental lines* of Schreger. A second system of dentinal striae, visible in ground sections of tooth under low magnification, are the *contour lines* of Owen (*arched incremental lines* of Salter). They run nearly parallel to the lines of Schreger in the crown and toward the tip of the root, but elsewhere cut these lines at wide angles (Fig. 314). They represent lines of defective calcification between successively deposited layers of dentin

The superficial portion of the dentin is formed by the *granular layer* of Tomes, in which there are no dentinal tubules, but instead there are in this layer

numerous small interglobular spaces from which minute canaliculi radiate in various directions. Many of these canaliculi are connected, on the one hand with the dentinal tubules, and on the other with the canaliculi and bony lacunae of the cementum. The canaliculi of the granular layer are readily distinguished from the adjacent dentinal tubules by the extreme irregularity of their course, which contrasts sharply with the straight or regularly curved course of the dentinal tubules.

The granular layer is relatively thick in the root of the tooth, but becomes much thinner toward the neck. Beneath the enamel it becomes so thin that toward the apex of the tooth it is scarcely demonstrable. At this point also, occasional dentinal tubules are continued for a short distance into the enamel, though this condition is more characteristically developed in some of the lower mammals (*e.g.*, Rodentia) than in man.

Enamel.—The enamel, which covers the exposed crown of the tooth, is the hardest tissue of the body. About 90 per cent of its earthy matter is calcium phosphate; about 4 per cent is calcium carbonate; less than 5 per cent of its substance consists of organic matter. It contains a slightly larger trace of calcium fluoride than dentin.

Its unit of structure is a calcareous cylinder, the *enamel prism*. These prisms or "fibers" radiate outward from the dentin and are disposed after the manner of a mosaic. They are firmly united to each other by a very thin layer of calcified *interprismatic cement substance* They represent calcified columnar ectodermal cells.

FIG. 319 —ENAMEL PRISMS IN TRANSECTION.

From the tooth of a calf. ×350 (Kölliker.)

In transverse section the enamel prisms have a polygonal, frequently quite regular hexagonal, outline. In certain bundles, especially toward the periphery, the prisms have the shape in transverse outline of stout crescents. In longitudinal view the prisms present a slightly beaded appearance, the constricted portions being darker and delicately cross-striped. This peculiar structure and optical condition results from the manner of the formation of the prisms by the deposition of successive globules of preënamel substance, subsequently becoming calcified to form definitive enamel. The enamel cement exhibits a reciprocal beading The striped and beaded character of the enamel prisms is specially conspicuous in the teeth of rodents

Since the external surface of the enamel is greater than the internal, and since the enamel prisms are of approximately uniform diameter throughout, additional shorter prisms, pointed at their inner end, are interpolated toward the surface. Such "supplementary prisms" have been described by various investigators, including Tomes ('14) and Noyes and Thomas ('21). von Ebner ('99) and Pickerill[3] have denied their occurrence. Pickerill gives the average proximal diameter of the enamel prisms as 3.1 microns, the average distal diameter as 5.7 microns. The most recent study in this field has been done by Chase.[4] He

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[3] Pickerill, 1913.

[4] Chase, 1924.

found no evidence of supplementary prisms in human dental enamel. He states that the increase in the surface of the enamel is accomplished almost entirely by increase in diameter of the prisms; a very minor factor in the increase of surface is due to the fact that some of the prisms meet the outer surface obliquely. The interprismatic substance is said to play no part in the increase of surface; and all the prisms in human dental enamel extend through the entire thickness of the enamel. Each prism is the product of a single ameloblast.
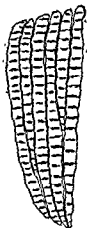
FIG. 320.—A GROUP OF ENAMEL PRISMS CUT LONGITUDINALLY FROM THE INCISOR TOOTH OF THE RAT, SHOWING THEIR IRREGULARLY BEADED CHARACTER AND THE CROSS-STRIATIONS

Shorter and slenderer prisms are interpolated peripherally. × 375

The enamel prisms are grouped into bundles within which the constituent prisms are parallel. The course of the prism bundles, however, is variable, so that, though following a more or less radial course through the enamel, the prism bundles frequently cross one another at acute angles. In axial longitudinal sections of ground tooth this crossed arrangement of the prism bundles produces the appearance of radially disposed alternating dark and light bands. This banding is seen under low magnification, and is especially conspicuous in reflected light; it is due to the difference with which the groups of transverse and longitudinally cut enamel prisms reflect the rays of light. The dark bands are known as the *radial lines*, or the *prism stripes* of Schreger.

Ground sections of dried tooth show also brownish lines in the enamel having an arrangement approximately parallel with the surfaces of the tooth. These *contour lines* of Retzius are explained by von Ebner as the result of air-filled fissures in the dried enamel. They are also said to be the result of the wavy direction of the enamel prisms. They are most probably caused by imperfect calcification, marking growth stages in the development of the enamel.

Cementum.—The *dental cement*, or *crusta petrosa*, is a thin layer of bony tissue which invests the root of the tooth. It forms a very thin layer at the neck of the tooth, but gradually increases in thickness as it approaches the tip of the fang.

The cementum consists of parallel layers of bony lamellae between which many lacunae with their bone corpuscles are included. Bone canaliculi radiate from the lacunae and frequently open into the interglobular spaces of the granular layer. There are no haversian systems in the cementum, but the thicker portions are frequently penetrated by vascular canals which, like Volkmann's canals, are not accompanied by concentric lamellae. The cementum is firmly united to the granular layer of the dentin, the matrix of the two tissues being continuous.

The cementum is invested with a periosteal coat, the periodontium, *pericementum*, alveolar periosteum, or *root (peridental) membrane*, of dense fibrous tissue. At the neck of the tooth it unites with the dense connective tissue of the gum to form an annular thickening of very dense fibrous tissue which encircles the

tooth and is known as the *circular dental ligament*. The root membrane contains no elastic fibers, but sends considerable numbers of slender collagenous fibrous bands (*Sharpey's fibers*) into the cementum. These bands effect a firm anchorage of
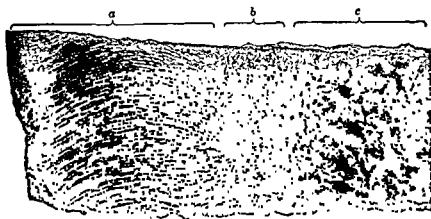
FIG. 321.—FROM A SECTION OF A HUMAN TOOTH WHICH HAD BEEN GROUND TO EXTREME THINNESS.

a, dentin; *b*, granular layer of Tomes, *c*, cementum. Photo. ×140.

the tooth to the alveolar wall. They are analogous to the perforating fibers of Sharpey which bind the periosteum to the osseous lamellae.

DEVELOPMENT

The teeth arise in part from the ectodermal epithelium of the oral cavity and in part from the mesenchyma of the alveolar processes. In the seventh week of fetal life there appears upon the surface of the maxillary ridges a thickening of the epithelium which grows into the subjacent mesenchyma in the form of a longitudinal plate or shelf, the *labiodental strand*, whose position is indicated superficially by a *dental groove* which indents the epithelial surface of the primitive gum. The labiodental strand divides at its deeper border into a nearly vertical continuation, the *labial lamina*, which subsequently becomes hollow to form the labiogingival groove; and a horizontal inwardly directed shelf, the *dental lamina*, which forms the earliest primordium of the enamel, the *enamel organ*.

At the beginning of the third month the dental shelf shows upon its deep margin a series of shallow inverted cups, one for each of the temporary teeth, produced by an up-pushing of a corresponding series of cone-shaped areas of condensing mesenchyma at the site of each tooth germ. Each mesenchymal thickening forms the primordium of a *dental papilla*. That portion of the dental shelf which spreads out laterally to cover the dental papilla of each tooth forms its *enamel germ*, from which the dental enamel is eventually produced. Further development of the enamel germ and dental papilla causes the former to sur-

round the papilla like a cap. Figures 322 and 323 show four stages in the early
development of a tooth.

During the third month of fetal life the primordia of all primitive (*deciduous,
milk,* or *temporary*) teeth are formed in the above manner. At about the same
time, also, a posterior growth upon the lingual side of the thin portion of the
dental shelf which still connects the enamel germs with the oral epithelium, forms
the primordia of twenty of the *permanent* teeth. The twelve additional permanent
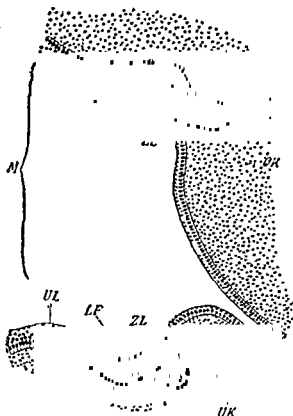
FIG. 322 —DEVELOPING TOOTH FROM A HUMAN EMBRYO 17 MILLIMETERS LONG.

LF, dental groove; *M,* oral cavity; *OK,* mesoblast of upper jaw; *UK,* primordium of lower
jaw; *OL,* epithelium of the primitive upper lip, and *UL,* of the lower lip; *ZL,* dental lamina
(labiodental strand). ×120. (Röse.)

molars arise at a later period and in a similar manner by a dorsal extension of the
dental lamina which grows backward through the connective tissue of the alveo-
lar process as a solid cell column from which the enamel germs are formed and
into which the dental papillae grow.

Further development of the dental primordium includes the differentiation of
the enamel germ on the one hand and of the dental papilla on the other. From
the former the enamel and the *cuticular epithelial membrane* arise; the latter pro-
duces the dental pulp and the dentin.

Enamel Germ.—The enamel germ or *enamel organ* soon differentiates into three layers: an *inner enamel epithelium* which forms the enamel prisms, an *outer enamel epithelium* which lines the dental sac and an intervening *enamel pulp*.

Inner Enamel Epithelium.—The innermost cells of the enamel organ, *viz.*, those which rest directly upon the dental papilla, soon become elongated and attain
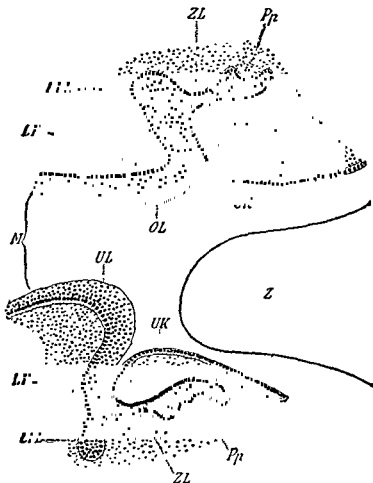
FIG. 323—DENTAL PRIMORDIA FROM A HUMAN FETUS 40 MILLIMETERS LONG.

Letters as in the preceding figure. *LFL*, labial lamina, or primordium of the groove between the lip and the mandibular process; *Pp*, dental papilla; *Z*, outline of the margin of the tongue; *ZL*, dental lamina ×60 (Röse.)

a cylindrical form. The nucleus moves toward the distal pole, and the original basal end becomes modified to take on the characteristics of the distal end of a columnar cell. A cuticular border appears upon the inner (originally basal) extremities, and as the calcareous substance of the enamel begins to be deposited fine processes are seen extending inward from the extremities of the enamel cells, *Tomes' processes.* It is around these processes that the permanent enamel is deposited first in the form of globules, which become calcified and meanwhile fuse to form the enamel prisms.[5]

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[5] Chase, 1932

The deposit of lime salts by the cylindrical cells of the inner enamel layer, *ameloblasts* (*adamantoblasts*), occurs earliest at the apex of the dental germ. Thus it is the enamel of the face of the tooth crown which is first formed, and this is therefore its thickest portion. The enamel on the sides of the tooth crown appears later and hence it gradually tapers in thickness as it approaches the neck of the tooth, *in which latter place the last formed enamel is found.*
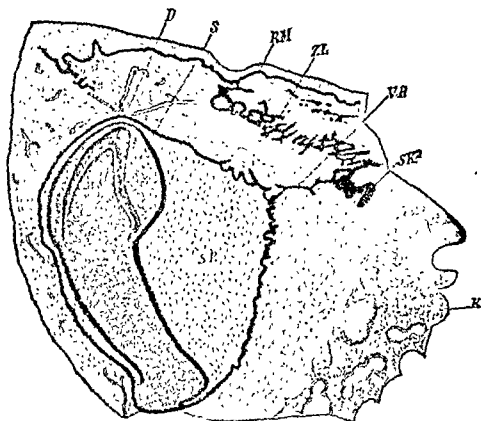
FIG. 324—DEVELOPING TOOTH FROM A HUMAN FETUS 30 CENTIMETERS LONG.

D, dentin; *K,* bone of the jaw, *RM,* germinal layer of the oral mucosa; *S,* enamel; *SK,* enamel primordium of the permanent tooth; *VB,* epithelial bridge still uniting the primordia of the temporary and permanent teeth; *ZL,* disintegrating dental lamina; *SP,* enamel pulp ×30. (Röse.)

The nucleated bases (originally apices) of the cylindrical cells of the inner enamel epithelium are also marked by a sharp cuticular margin and rest upon the adjacent cells of the enamel pulp, the innermost cells of which retain a characteristic epithelial appearance, and comprise the *stratum intermedium.* The thin layer formed by the uncalcified bases of the adamantoblasts, which still cover the free surface of the enamel at the eruption of the tooth, remains as the highly cornified *dental cuticular membrane* (of Nasmyth). This is soon lost by reason of mechanical wear.

According to Chase's [a] interpretation the Nasmyth's membrane, in its most com-

[a] Chase, 1926.

plete form, is derived from remains of the entire enamel organ excepting the enamel pulp, together with overlying layers of cells from the gingival epithelium. He divides this membrane into two portions: an inner pellicle, which is formed
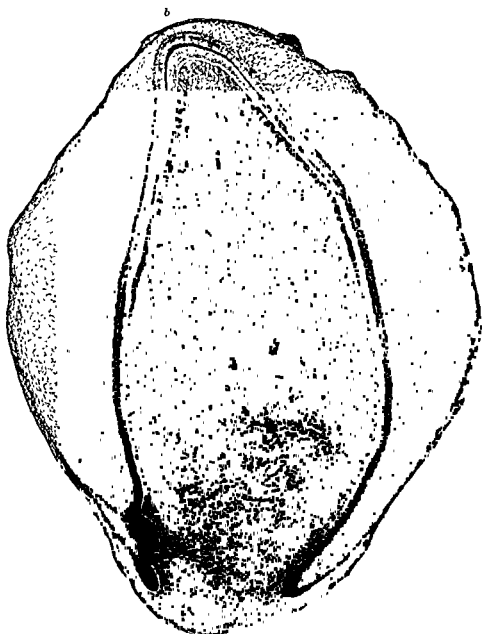
FIG. 325—A DEVELOPING TOOTH FROM AN INFANT'S JAW.

a, papilla; *b*, crown, *c*, outer enamel epithelium. Hematein and eosin. Photo. ×65.

. from the fused modified cuticular borders of the ameloblasts; and an outer cellular portion. The latter is said to comprise the remains of the enamel organ and cells from the gingival epithelium.

Outer Enamel Epithelium.—The outermost cells of the enamel germ are immediately in contact with the mesenchyma of the primitive jaw. This connective tissue

forms, toward the end of the third month, a vascular investing sheath or *dental sac*, which incloses the entire dental germ. Finally, by gradually encroaching upon the narrow neck which still connects the enamel germ with the dental lamina, it severs the connection of these organs so that the primitive tooth lies free within the dental sac. The outer enamel epithelium, which lines all portions of the dental sac except at the base of the dental papilla, forms several layers of flattened epithelial cells. Remnants of this cell layer frequently persist, in relation to the inner margin of the bony alveolus whose wall is produced by intramembranous ossification in the connective tissue surrounding the embryonic dental sac.

FIG. 326—A PORTION OF FIGURE 325, NEAR THE APEX OF THE DEVELOPING TOOTH.

a, enamel pulp; *b*, ameloblasts; *c*, enamel; *d*, dentin; *e*, odontoblasts; *f*, border of the dental pulp Between the formed enamel and the ameloblasts, Tomes' processes can be seen. ×550.

Enamel Pulp.—This structure is produced by a remarkable differentiation which occurs within the midportion of the enamel organ. The epithelial cells of this region, which at first appear to form a delicate syncytium, become separated by wider and wider intercellular spaces, and are thus drawn out into stellate forms with long anastomosing processes. The resulting cells closely resemble in form the connective tissue cells of embryonic or gelatinous connective tissue. This explains the designation *stellate reticulum*. They are, however, inclosed on all sides by the epithelial cells of the inner and outer enamel epithelium and, like other epithelial tissues, are never except in the case of the molar teeth penetrated by blood vessels [7,8,9].

The enamel pulp appears to serve a purely mechanical function, it being a soft tissue through which the growing tooth readily pushes its way to the surface.

Dental Papilla.—The dental papilla is a mesenchymal structure which is invested by and grows into the enamel organ. Coincident with the appearance of the ameloblasts in the enamel organ, the superficial cells of the dental papilla become enlarged, elongated, and so arranged as to form a continuous layer of odontoblasts on the surface of the papilla. These cells apparently secrete a thin homogeneous layer, *membrana preformativa* (Raschkow), which serves as a

[7] Jordan, 1921.
[8] Addison and Appleton, 1922.
[9] Jordan, 1923

basement membrane upon which the ameloblasts deposit the enamel prisms; it also forms the primordium of the granular layer of Tomes.

The odontoblasts now form the *dentin* in a manner entirely analogous to the deposit of bone by the osteoblasts, processes of the odontoblasts being included within the deposit of dentin to form the *dentinal fibers.* Irregular spaces, occurring in the dentin and granular layer, in which no calcification occurs produce the *interglobular spaces.*

The central mass of the dental papilla develops the reticular tissue of the *dental pulp.* The blood vessels and nerves enter the pulp through the base of the papilla, which thus becomes the primordium of the *root canal.*

The *cementum* is formed by intramembranous ossification occurring in that portion of the dental sac which invests the base of the dental papilla and the primitive root of the tooth.

The process of cementogenesis is essentially similar to that of perichondrial ossification. The vascular mesenchyma of the dental sac breaks through the epithelial sheath (the root extension of the enamel organ), and through the agency of modified mesenchymal cells similar to the osteoblasts, the *cementoblasts,* deposits cementum upon the dentin of the root. The first deposit is made in the neck region, and the deposition progresses thence to the apex of the root, where the thickest layer is subsequently found. Cementoblasts become inclosed in lacunae of the cementum and persist as *cementum* cells. The peripheral layer of the root portion of the sac differentiates into a dense fibro-elastic lamina which serves both as a pericementum to the tooth, and as periosteum to the bone of the jaw. The pericementum includes besides cementoblasts also *odontoclasts* which become active as tooth destroyers at about the age of five years. They absorb the roots of the deciduous teeth, and thus open the way for the eruption of the permanent teeth.
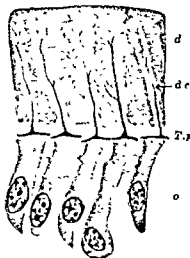
FIG 327.—ODONTOBLASTS AND DENTIN OF THE TOOTH OF A NEWBORN CAT.

o, odontoblasts; *Tp,* Tomes' fibrils, prolongations of the odontoblasts; *dc,* dentinal canal in the dentin (*d*). ×500. (Prenant, Bouin and Maillard.)

THE TONGUE

The tongue consists essentially of a mass of voluntary muscle invested by a continuation of the mucous membrane of the mouth and pharynx. The fibers of this striated muscle are separated into two lateral halves by a median septum of dense areolar connective tissue which extends from the base to the tip of the organ, and is known as the *lingual septum.*

Muscle Fibers.—The muscle fibers include two groups: the *intrinsic,* those of the *lingualis* or tongue muscle proper, and the *extrinsic,* those entering from without and serving to attach the tongue: the genioglossus, the hyoglossus, the

styloglossus, the palatoglossus and the chondroglossus. The fibers are disposed in three planes and are so arranged that the bundles cross one another at right angles. They thus form: (1) sagittal or vertical fiber bundles which are slightly inclined outward from the septum linguae and are derived from the lingualis muscle, supplemented in the inferior median portion by fibers from the genioglossus and the hyoglossus; (2) longitudinal fibers peripherally distributed and
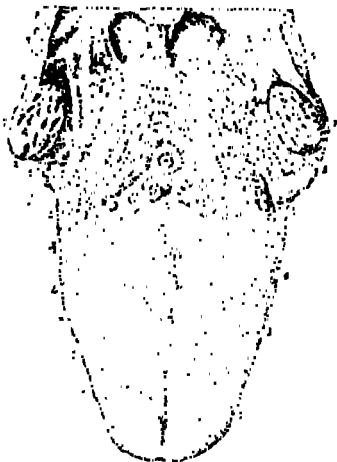
FIG 328—VIEW OF DORSUM OF TONGUE, SHOWING THE VARIOUS PAPILLAE, THE TONSILS AND THE FAUCES

1, circumvallate papillae, *2*, foramen cecum; *3*, fungiform papillae; *4*, filiform papillae; *5*, transverse and oblique rugae; *6*, mucous glands; *7*, tonsils; *8*, tip of epiglottis; *9*, median glosso-epiglottidean fold; *1*, foliate papillae; *L*, lenticular papillae. (Sappey.)

running from the base to the apex of the tongue, derived chiefly from the lingualis but supplemented on the under surface by the styloglossus, and chondroglossus; (3) transverse or horizontal fibers extending laterally from the septum linguae, which are also derived from the lingualis muscle, and include a few fibers from the palatoglossus.

The interlacing bundles of muscle fibers are embedded in loose areolar and adipose tissue. The muscle fibers are inserted into the corium of the lingual mucous membrane, their sarcolemma being firmly adherent to the connective tissue

of the mucosa, which invests the rounded blunt extremity of the muscle fiber. Many of these muscle fibers are branched.

Mucous Membrane.—The mucous membrane of the tongue consists of a thick corium, and an epithelial covering. The deeper part of the *corium*, consisting of loose areolar tissue, is intimately connected with the muscle. The superficial portion of the corium, containing denser areolar tissue, carries upon its surface dorsally connective tissue *papillae* of unusually large size which project into the
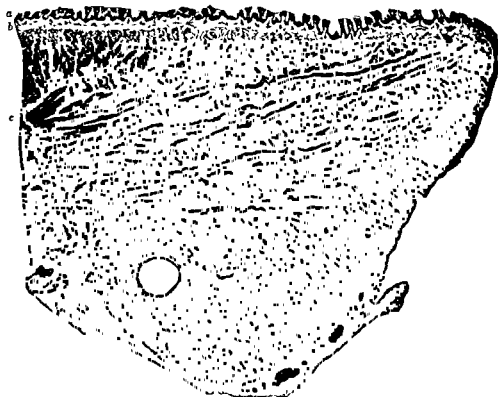
FIG. 329—ONE LATERAL HALF OF A CORONAL SECTION OF A DOG'S TONGUE.

The dorsal surface presents numerous large filiform papillae. *a*, lingual papillae; *b*, corium; *c*, the fibromuscular substance of the tongue. Hematein and eosin Photo ×6.

epithelial coat. The surface of the larger of these papillae is not smooth, but is covered with small *secondary papillae*.

The dorsal surface of the tongue presents a sharp structural difference between its anterior and posterior portions. The papillae are limited to the anterior portion, which includes about two-thirds of the entire surface; this is known as the *papillary area*. The posterior one-third lacks papillae, and is of lymphoid character, hence known as the *lymphoid* area (lingual tonsil). These two areas represent the originally separate primordia from which the definitive tongue develops: the anterior group including the paired lateral tongue primordia and the median unpaired *tuberculum impar*, and the posterior the paired *radices linguae*. The line of fusion is indicated in the fetus and infant by a shallow V-shaped groove, the sulcus terminalis. This subsequently disappears, and the

boundary then remains marked by the position of the circumvallate papillae. The papillary area constitutes the tongue proper.

Epithelium.—The epithelium of the tongue is of the stratified squamous variety. Upon the under surface and margins of the organ its surface is smooth, but on the dorsum of the tongue the stratified epithelium forms tall projections, which correspond with the papillae of the corium, and which constitute the so-called *lingual papillae.* These papillae are of three varieties: conical or filiform, fungiform and circumvallate.

CONICAL OR FILIFORM PAPILLAE.—These papillae consist of flattened and elongated epithelial cells which are often so arranged as to produce a slender conical projection or epithelial tuft of variable height, which covers the apex
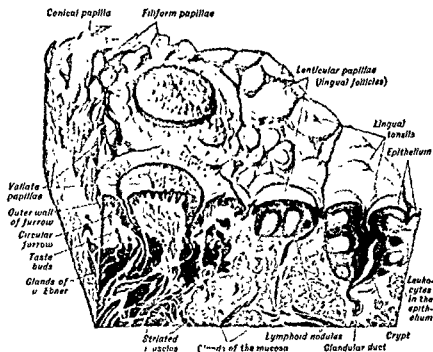
FIG 330—SURFACE OF THE TONGUE AT THE BORDER BETWEEN THE ROOT AND THE DORSUM. ×16. (Braus)

of each connective tissue papilla. This type is the most abundant of the three varieties of lingual papillae. They are found upon all portions of the dorsum of the tongue They range in height from 0.5 to 2.5 millimeters.

FUNGIFORM PAPILLAE.—The fungiform papillae are formed by a large connective tissue papilla or core which projects above the general level of the epithelial surface and is covered by a smooth layer of stratified squamous epithelium in which occasional taste buds are found. This variety, though much less abundant than the former, is still numerous and may be found upon any or all portions of the dorsum of the tongue, where they are irregularly scattered among the filiform papillae. The fungiform variety are most abundant near the margin of the tongue on its dorsal surface Their maximum height is about 1.5 millimeters.

CIRCUMVALLATE PAPILLAE.—The circumvallate papillae form a group of from eight to twelve elevations which are situated at the base of the tongue, and are arranged in the form of a V, the apex being directed toward the larynx. These papillae are much broader (2 to 3 millimeters) than either of the former varieties. They extend slightly above the general level of the epithelial surface, are of an inverted conical shape, and are covered by a smooth layer of stratified squamous epithelium. Their base is surrounded by a deep circular excavation, lined by an invagination of the layer of stratified epithelium, which thus forms a deep trench about the base of the papilla.

The epithelium which covers the sides of the circumvallate papillae, as well as that forming the lateral wall of the trench contains large numbers of *taste buds* (see Chapter VI). The large central connective tissue papilla carries upon its surface many small secondary papillae of the corium, which project into the epithelial coat of the circumvallate papilla upon its free surface, but are not found upon its lateral margins.

The mean number of taste buds on the circumvallate papillae between birth and the twentieth year is said to be remarkably constant, approximately 245. The number declines to 88 in extreme old age.[10] The taste buds are variable in size and shape. They are not formed on the top surface of the papillae and only rarely in the floor of the trench. In rare instances two or three papillae may be surrounded by a single trench.

FIG. 331.—A FILIFORM AND A FUNGIFORM PAPILLA, FROM AN INJECTED SPECIMEN OF TONGUE OF CAT.

On the lateral margins of the tongue, just in front of the anterior pillars of the fauces, occur a variable number of transverse parallel folds or leaves, the *foliate papillae*. These are only slightly developed in man, but are well developed in the rabbit and certain other rodents. They contain numerous taste buds. In the lymphoid area also, at the anterior lateral margins, are a group of low irregularly disposed mucous folds, the so-called *lenticular papillae*.

Mucous and *serous* glands occur in the deeper portion of the corium of the tongue and among its muscle bundles; they open upon its epithelial surface between the papillae. These glands are most abundant at the base of the organ but are also found along its margins as far forward as the tip, where a pair of

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[10] Arey, Tremaine and Monzingo, 1935.

small tubulo-acinose seromucous glands lie on either side of the median septum and open upon the ventral surface of the tongue. These are the *anterior lingual glands* of Nuhn. The *serous glands* of von Ebner are confined to the region of circumvallate papillae at the base of the tongue. They pour their secretion into the trench which surrounds the base of the papilla or into the crypts of the lingual tonsil. Other lingual glands, of the small tubulo-acinose mucous type, occur at various portions of the dorsal surface of the tongue, being especially abundant in the lymphoid area.

Lingual Tonsil.—The lingual tonsil (Fig. 255) is a considerable collection of lymphoid nodules which is found at the base of the tongue in and about the median line. These nodules are grouped about a large funnel-shaped crypt, the *foramen cecum*, which opens at the apex of the V formed by the group of
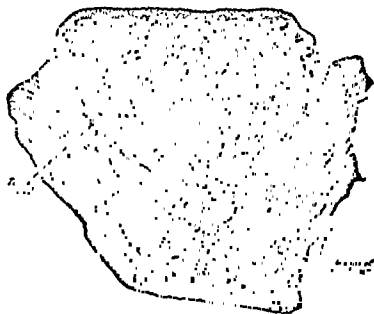
FIG. 332.—CIRCUMVALLATE PAPILLA OF HUMAN TONGUE. ×55.

circumvallate papillae and which in the embryo forms the lingual extremity of the so-called duct of the thyroid gland (*thyroglossal duct*). Several smaller crypts are also included in the region of the lingual tonsil.

The lymphoid nodules are embedded in the mucosa or corium of the tongue and are surrounded by mucous glands, many of whose ducts penetrate between the nodules to open into the branching crypts. Lymphocytes, apparently derived from the nodules, infiltrate the surrounding connective tissue and epithelium and find their way into the lumen of the tonsillar crypts.

Blood Vessels.—The blood vessels of the tongue are supplied by large arteries (branches of the lingual artery) which, with the corresponding veins, are embedded in the muscular portion of the organ and supply capillary vessels to this tissue. From these arteries, also, small arterial branches enter the deeper portion of the corium and form a capillary plexus which supplies the connective tissue

and whose terminal ramifications extend to the very apex of the connective tissue papillae. The blood is returned by veins which pursue a similar course.

The tongue of the dog is characterized by the occurrence of numerous arterio-venous anastomoses (canals of Sucquet-Hoyer), presumably connected in some way with elimination of heat upon a rise of body temperature.[11] These vascular glomi have a rich nerve supply, including thin unmyelinated fibers with terminations in the media of the S-II canal and thick myelinated fibers with terminations mainly located in the adventitia.

Lymphatics.—The lymphatics form a superficial set of small vessels and tissue spaces beneath the epithelial layer, which are especially abundant in the region of the lingual tonsil at the base of the tongue. The lymphatic vessels of this superficial plexus frequently encircle the lymphoid nodules. A deeper plexus of lymphatics in the loose connective tissue of the submucosa receives the lymph from the superficial plexus and conveys it by efferent lymphatic vessels to the deep cervical lymphatic glands.
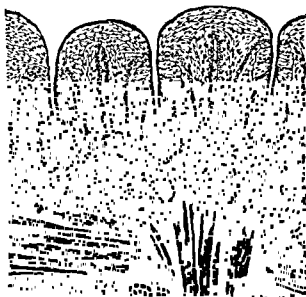
FIG. 333.—TWO FOLIATE PAPILLAE FROM A RABBIT'S TONGUE, SHOWING NUMEROUS TASTE BUDS ALONG THEIR LATERAL MARGINS. ×108.

Nerve Supply.—The nerve supply of the tongue comprises cerebral, both sensory and motor fibers, and sympathetic fibers. The sympathetic elements supply the glands and blood vessels; small ganglia occur along their course. The motor fibers supplying the striped muscle are derived from the hypoglossal nerve. These end in motor end-plates. The sensory fibers arise from the lingual branch of the trigeminal and the glossopharyngeal nerves. These mediate both general sensibility and the sensation of taste. The fibers which receive the stimuli of general sensibility end as naked varicose fibrils in the connective tissue of the body of the tongue, and in the submucosa of the papillae. They are accompanied by small ganglia. Certain fibers also end in muscle spindles. The fibers of special gustatory sensation are also distributed to the papillae; the chorda tympani (branch of the facial) component of the lingual branch of the trigeminal supplying the anterior two-thirds, the glossopharyngeal the posterior one-third of the tongue. At the base of the tongue small nerve bundles of taste fibers are distributed to the circumvallate papillae, and form a subepithelial plexus from which fibrils are distributed: (1) to the interior of the taste buds where they end in relation with the gustatory cells, *intragemmal fibers;* (2) to the surface of the taste buds, *perigemmal fibers;* and (3) to the intervening portions of the epithelial layer, where they end between the epithelial cells as in other parts of the tongue, *inter-*

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[11] Brown, 1937

gemmal fibers (Fig. 185). The taste buds of the soft palate are innervated through the palatine nerves (great superficial petrosal component) of the trigeminal.
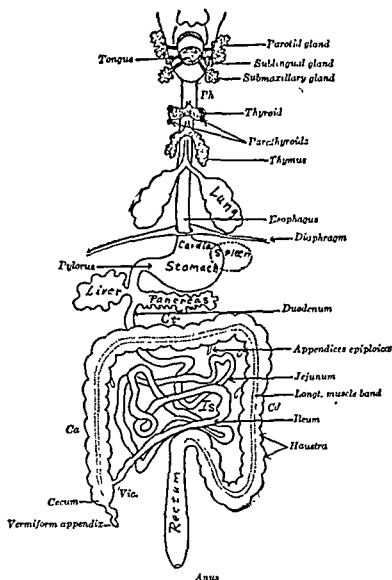
FIG. 334—DIAGRAM OF THE ALIMENTARY CANAL OF MAN.

Is, small intestine; *Ca*, *Ct*, and *Cd*, ascending, transverse and descending portions of the colon; *Ph*, pharynx; *Vic.*, ileocecal valve. (Adapted from Wiedersheim.)

THE ALIMENTARY CANAL

CHARACTERISTICS OF THE WALLS

It is convenient to consider collectively under this head the pharynx, esophagus, stomach and the small and large intestines. This tract forms a continuous tube

whose wall has, throughout its entire extent, many common characteristics. Thus the wall in all portions consist of four coats which are respectively known, from within outward, as the mucous, submucous, muscular and fibroserous. The three outermost coats are of very similar structure in all portions of the tract.

Fibroserous Coat (Tunica Fibroserosa).—In the abdominal cavity the outermost coat is derived from the peritoneum, by which the stomach and intestines are invested. In the upper portion of the tract, pharynx and esophagus, the serous coat is replaced by a layer of areolar connective tissue, constituting a *tunica fibrosa*, which usually contains much fat. In the abdomen the homologous subserous connective tissue is covered by a layer of mesothelium. The connective tissue of the outer fibroserous coat contains the larger blood and lymphatic vessels whose branches are distributed to the three inner coats.

Muscular Coat.—The muscular coat (*tunica muscularis*), situated next within the fibroserous, is divisible into two layers, an outer longitudinal, the direction of whose fibers is parallel to the long axis of the canal, and an inner transverse layer whose fibers are circularly disposed. The two layers are united by a thin septum of areolar connective tissue which serves for the support of the larger blood vessels and lymphatics, whose capillaries are distributed to the muscular coat. This septum also contains a coarse-meshed nerve plexus, consisting of small anastomosing nerve trunks which are composed in large part of unmyelinated fibers, at whose intersections are numerous small sympathetic ganglia, the *myenteric* (*Auerbach's*) *plexus* and *ganglion*.

Below the level of the junction between the middle and lower third of the esophagus, and including the musculature of the stomach and intestines, the muscle is entirely of the nonstriated or smooth variety. In the pharynx and upper third of the esophagus, the striated or voluntary type of muscle is exclusively found. In the midpor-

FIG. 335.—SURFACE VIEW OF AUERBACH'S INTRAMUSCULAR NERVE PLEXUS, FROM THE ESOPHAGUS OF A CAT

Methylene blue ×40 to 50 (De Witt)

tion of the esophagus both striated and nonstriated muscle occur in varying proportions, occasional striated fibers being found even in the lower third of the organ.

Submucous Coat.—The submucous coat (*tela submucosa*) consists of loose areolar tissue, and serves for the support of the larger blood and lymphatic vessels which supply this coat and the mucosa. A second plexus of nerve fibers, similar in structure to the intramuscular plexus, is found in the deeper layers of the submucosa, and is known as the *submucous* (*Meissner's*) *plexus*. Its nerve trunks and ganglia are somewhat smaller than those of the myenteric plexus. The submucous plexus supplies the muscular and glandular tissues of the mucous membrane.

Mucous Membrane.—The mucous coat or mucosa (*tunica mucosa*) of the gastro-intestinal canal contains four typical structures: (1) an internal lining epithelium attached to a distinct basement membrane (membrana propria); (2) the lamina muscularis mucosae which forms the outermost layer; between these is (3) a lamina propria mucosae or corium of diffuse lymphoid or areolar tissue, which serves chiefly for the support of (4) the secreting glands.

The *lamina muscularis mucosae* usually consists of a double layer of smooth muscle, the outer being longitudinally, the inner circularly disposed. This layer is most highly developed in the esophagus.

The *lamina (tunica) propria* consists of delicate fibro-elastic and reticular tissue whose volume is in inverse proportion to that of the secreting glands. It is most abundant in the esophagus. *In the stomach and intestines it is considerably infiltrated by lymphocytes and often contains diffuse lymphoid tissue.* Small lymph nodules are also found in the deeper part of this membrane; they progressively increase in size toward the lower portion of the tract, where they form the solitary nodules of the intestine.

The nature of the lining epithelium and the type of glands differs in each succeeding portion of the canal, and must, therefore, together with the other peculiarities of the several subdivisions of the tract, be separately considered.

THE PHARYNX

The pharynx may be subdivided, upon histological as well as physiological grounds, into (1) an upper respiratory portion, or nasopharynx, and (2) a lower portion, oropharynx and laryngopharynx. Only the laryngopharynx properly belongs to the alimentary tract. The soft palate and uvula form a thin partition between the naso- and oropharynx. The nasopharynx has already been described as a part of the respiratory system (see Chapter XII).

The mucous membrane of the lower portion of the pharynx is lined with stratified squamous epithelium which rests upon a thick corium of areolar tissue. The lamina propria is well supplied with thin-walled blood vessels and lymphatics, and contains many mucus-secreting glands of the tubulo-acinose type whose secreting portions lie deeply embedded in the connective tissue of the muscular coat.

There is no lamina muscularis mucosae in the mucous membrane of the pharynx; its place is taken by a layer of connective tissue which is exceedingly rich in longitudinal elastic fibers. This layer lies immediately upon the muscular coat, into which processes of fibro-elastic tissue extend between the muscular bundles; hence this fibro-elastic layer also serves as a submucosa.

The superficial layer of the corium contains diffuse collections of lymphoid tissue and occasional small lymph nodules.

The muscular coat of the pharynx is formed by its constrictor muscles. Their striated fibers mostly pursue an oblique course. Where these muscles are not immediately attached to the periosteum of the vertebrae, the pharynx is invested with an outer coat of areolar connective tissue by which it is loosely united to adjacent organs.

ESOPHAGUS

The *esophagus* or *gullet* is a short tube about 25 centimeters (10 inches) in length, connecting the pharynx with the cardia of the stomach. Its wall contains the usual four coats · the outer fibrous, muscular, submucous and mucous (Fig. 337).

Outer Fibrous Coat.—The outer fibrous coat envelops the wall of the esophagus and unites it to the adjacent organs. It consists of loose fibrous tissue, and contains the blood and lymphatic vessels and nerve trunks which supply the three inner coats. It is not invested by a serous layer.
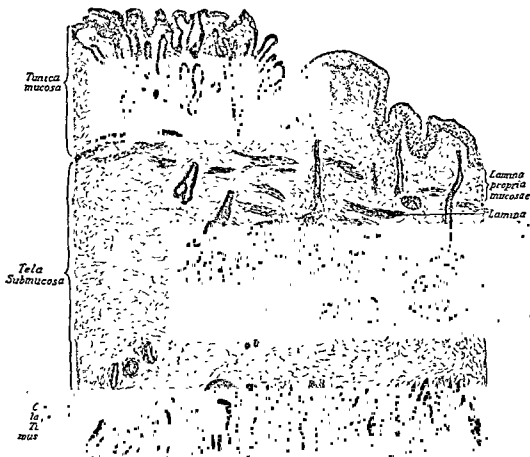
FIG 336.—LONGITUDINAL SECTION THROUGH REGION OF TRANSITION FROM ESOPHAGUS (RIGHT)
TO CARDIAC END OF STOMACH (LEFT).

Muscular Coat.—The muscular coat contains an outer longitudinal and an inner circular layer of muscle fibers, which are separated by a narrow septum of loose areolar tissue. In the upper third of the esophagus the muscle is of the striated variety, in the middle third it is mixed, in the lower third it is generally smooth. The distribution of the muscle in the lower third is subject to great individual variation, and occasional striated fibers are often found all the way down to the diaphragmatic opening.

The areolar septum between the muscular layers contains the larger blood vessels and the myenteric nerve plexus and ganglia.

Submucous Coat.—The submucous coat forms a layer of areolar connective tissue which firmly unites the muscular and the mucous coats. It contains those blood and lymphatic vessels, together with the submucous nerve plexus, whose branches supply the mucous membrane. It also contains a considerable number of tubulo-acinose mucous glands whose ducts enter the mucous membrane and open upon the free epithelial surface. The secreting acini of these glands are short
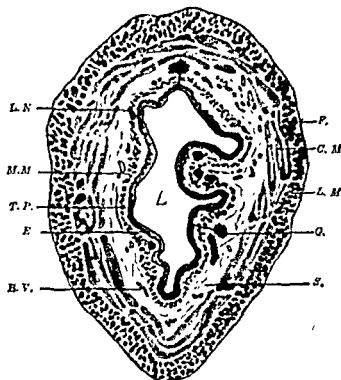
FIG. 337.—TRANSVERSE SECTION OF HUMAN ESOPHAGUS THROUGH LOWER THIRD.

L, lumen; F, fibrous tunic; C. M., circular muscle layer; L. M., longitudinal muscle layer; G, mucous glands in submucosa (S); L. N., lymph nodule; M. M., lamina muscularis mucosae; T. P., lamina propria mucosae; E, stratified squamous epithelium; B. V., blood vessels. (Adapted from Merkel.)

branching tubules with ampullary dilatations; they possess a characteristic, tortuous form. Their columnar secreting cells have a strong affinity for muchematein and other specific stains for mucus. This basophil reaction, together with the situation of their isolated groups of secreting acini *in the submucosa*, sharply distinguishes the esophageal mucous glands from the glands of the stomach and intestine, except those of the duodenum.

The number of the esophageal glands in man is extremely variable. This numerical variability is associated with frequent cyst formation, stasis of secretion, and atrophy of the glandular elements; conditions indicating small functional significance In certain mammals, e.g., rodents, ox, horse, sheep, cat and bat, glands are entirely lacking; in others, e.g., opossum, dog and pig, they are very abundant.

Except in man, the mucous alveoli contain demilunes. Esophageal glands are the exception rather than the rule in mammals. The fact that they are absent in all vegetable feeders but present in mixed feeders indicates that they have a chemical rather than a mechanical function [12]

Mucous Coat.—The mucous coat (*mucosa*) of the esophagus consists of a lamina propria or corium of areolar tissue which rests upon a well-developed lamina muscularis mucosae and is covered on its free surface by stratified squamous epithelium.

The lamina muscularis mucosae consist of bundles of smooth muscle cells arranged longitudinally. In the upper third of the esophagus it may be incomplete, or it may even be lacking; in the lower third it may include, as it does elsewhere in the digestive tube, a less robust inner layer of circularly disposed muscle.

The inner portion of the lamina propria carries on its surface many tall connective tissue papillae which project well into the epithelial coat and which closely resemble the vascular papillae of the skin (Fig. 338).

The midportion of the corium is penetrated by the excretory ducts of the mucous glands. These are at first lined by low columnar cells which, as they approach the epithelial surface, are changed into several layers of flattened cells, which thus form a thin stratified lining, continuous with the superficial stratified squamous epithelium of the esophageal mucosa. Many of these ducts possess small cystic dilatations which are found in the connective tissue of the corium or occasionally in the submucosa

Superficial Glands.—At about the level of the cricoid cartilage the esophageal mucous membrane presents two lozenge-shaped depressions, one on either side, whose diameter varies from 1 centimeter down to microscopical size. These areas mark the site of the *superficial glands* of the esophagus (Hewlett) or *upper cardiac glands* (Schäfer). These are short branched tubular glands which closely resemble those of the cardiac region of the stomach
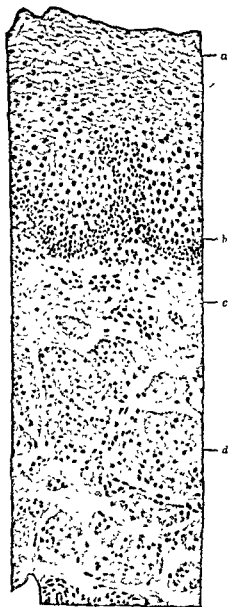
FIG. 338.—FROM A SECTION OF THE HUMAN ESOPHAGUS.

a, slight cornification of surface epithelium; *b*, stratum germinativum; *c*, lamina propria mucosae; *d*, lamina muscularis mucosae. (Goetsch.)

They are confined to the mucous membrane; their tubules, in marked contrast to those of the deep mucous glands of the esophagus, never penetrating the muscularis mucosae, which, however, is considerably thinned beneath the superficial glands. These glands secrete a mucinous fluid, but their cells are not so strongly basophilic as those of true mucous glands such as the deep glands of the esophagus. Both the ducts of the superficial glands and their secreting portions are lined with columnar epithelial cells. The lining epithelium of that part of the esophagus upon which the ducts open also consists of columnar cells. Many of the secreting tubules contain parietal cells similar to those of the fundic glands of the stomach. Both ducts and secreting tubules contain small, cystic dilatations.

At the lower end of the esophagus a similar group of superficial glands, the *lower cardiac glands* of the esophagus, frequently mark the beginning transition to the structure of the cardiac portion of the stomach, with whose glands they are continuous.

The lining epithelium of the esophagus is of the stratified squamous variety. Its attached surface is indented by the papillae of the corium; its free surface is smooth. In the collapsed state of the organ its mucous membrane is thrown into longitudinal folds or rugae and its lumen is largely obliterated. The small isolated areas of columnar or ciliated epithelium, which occur in occasional individuals on the surface of the esophageal mucosa, especially in its upper third, are to be regarded as examples of irregular development, involving a persistence of the ciliated areas occurring, according to *Johnson*,[18] in embryos ranging from 55 millimeters to birth.

THE STOMACH

Serous Coat.—The serous coat (*tunica serosa*) of the stomach is derived from the peritoneum. It is formed by a thin layer of subserous connective tissue which is covered with mesothelium. The serous coat supports the larger blood and lymphatic vessels and nerve trunks which supply the organ

Muscular Coat.—The muscular coat of the stomach consists in general of two layers of smooth muscle fibers—a thin outer longitudinal, and a much thicker inner circular and oblique layer. The regular circular arrangement of these fibers is much distorted by the peculiar dilatation and partial rotation to which the stomach is subjected in the course of its development, and as a result of this change obliquely placed fibers form a considerable portion of the muscular coat.

The oblique fibers are most numerous toward the cardiac end of the stomach, where they form a third muscular layer, the innermost portion of the muscular coat. The longitudinal fibers are most abundant toward the cardiac and pyloric orifices and along the lesser curvature; in the fundus and midregion of the stomach they form only a very thin layer. The circular fibers form the thickest of the three muscular layers and are nearly equally distributed in all portions, except that

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at the cardiac and pyloric orifices they become much thickened to form the sphincter muscles. The pyloric sphincter is especially well developed.

The layers of the muscular coat of the stomach are united by thin septa of connective tissue. That between the longitudinal and circular layers contains the myenteric nerve plexus and ganglia, and the larger blood vessels which supply this coat.

FIG. 339.—SECTION THROUGH THE STOMACH WALL OF MAN (PYLORIC REGION). ×14.

Submucosa.—The tela submucosa consists of loose areolar tissue which supports the blood vessels, lymphatics, and the submucous nerve plexus, all of which distribute their branches to the mucous membrane. In no portion of the stomach does this coat contain glands.

Mucous Coat.—The lamina muscularis mucosae forms a thin but complete layer from one end of the stomach to the other, and marks the outer boundary of the mucous membrane. It usually consists of two thin layers, an inner circular and an outer longitudinal. Here and there muscle fibers extend from the muscularis mucosae into the corium between the gastric glands.

The surface of the tunica mucosa is clothed with tall columnar epithelium, and the whole membrane is thrown into wavy folds, an arrangement which is permitted by the very loose character of the submucous areolar coat. The corium of the mucosa is closely packed with tubular secreting glands, which open on the

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[13] Johnson, 1910.

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Tunica mucosa

Tela submucosa

Tunica muscularis

A. Massie

Tunica serosa

FIG 339 —SECTION THROUGH THE STOMACH WALL OF MAN (PYLORIC REGION). ×14.

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of the fundus, where they form a complete lining for the tubule. In this portion the parietal cells are crowded away from the lumen and consequently produce a bulging of the basement membrane. Toward the neck of the tubule the parietal cells are more abundant and draw progressively nearer the lumen until, in the neck of the gland, they possess a considerable free surface which encroaches upon the glandular lumen.

THE CHIEF CELLS (CENTRAL, PEPTIC, or ADELOMORPHOUS CELLS).—The chief cells possess a columnar or pyramidal shape and a granular cytoplasm. The spheroidal nucleus is situated in the proximal or attached end, while the distal end of the cell is its most granular portion. The breadth of the granular zone is dependent upon the state of secretory activity, the coarse zymogen granules accumulating during periods of rest and disappearing by secretion during activity. Thus the granular distal zone increases in breadth during rest and decreases during activity. The whole cell also, becomes shrunken after prolonged secretion, but during rest it becomes so swollen that with its neighbors it nearly occludes the lumen of the tubule.

The coarse *zymogen granules* within the cell appear to be suspended within the meshes of a finely granular cytoplasmic reticulum. At the base or proximal end of the cell coarse elongated granules or filaments of *prozymogen* (ergastoplasm of Cade) may be demonstrated by the stronger basic or nuclear dyes, *e.g.*, iron hematein, toluidine blue. These peculiar prozymogen granules are so disposed, parallel to the axis of the cell, as to give this portion of the cytoplasm a somewhat striated or rodded appearance when carefully examined after suitable staining. The chief cells are believed to elaborate the pepsin (pepsinogen) of the gastric juice.

THE PARIETAL CELLS (OXYNTIC or DELOMORPHOUS CELLS.—The parietal cells are large ovoid or pyramidal bodies which are frequently binucleated, and whose cytoplasm possesses a strong affinity for acid dyes (eosin, Congo red, etc.). Their spherical nuclei contain much chromatin and are centrally situated; their cytoplasm is homogeneous or finely granular

The shape of the oxyntic cells varies with their location At the fundus of the

FIG. 341.—LONGITUDINAL SECTION OF THE FUNDUS GLANDS OF MAN.

b, parietal cells; *g*, fundus of the gland, *h*, chief cells, *k*, body, and *l*, neck of the gland, *m*, lamina muscularis mucosae, *Mg*, gastric crypts. ×85. (*Kölliker*.)

surface by wide-mouthed, crypt-like ducts or foveolae, and are embedded in a fine fibroreticular tissue containing many lymphocytes.

The lining epithelium of the stomach lacks typical goblet cells. However, the columnar cells contain mucin or mucinogen in the form of granules and globules. Accordingly, this epithelium is mucus secreting in function, the mucus having a protective and lubricating purpose.

The character of the *gastric glands* differs somewhat in various portions of the stomach. The three varieties, according to their distribution, are known as the fundic glands, the pyloric glands, and the cardiac glands.

Fundic Glands (Peptic Glands).— These are somewhat branched tubular glands which possess short ducts, the *crypts* or *foveolae*, and relatively long secreting portions, several of which open, by means of short constricted portions, the *necks* of the glands, into the bottom of each crypt.

The excretory ducts or crypts are lined with tall columnar cells which possess a remarkably clear cytoplasm distally, and whose nuclei lie at the proximal or attached ends of the cells. This epithelium rests upon a distinct basement membrane of reticular tissue. It is also continued over that portion of the corium which occupies the intervals between adjacent ducts, where it forms the true *lining epithelium* of the stomach. Its cells secrete a clear muco-albuminous fluid. Between the distal ends of the cell terminal bars occur. These cells possess also indistinct cuticular borders.

FIG 340—VERTICAL SECTION OF SECRETORY PORTION OF A FUNDIC GLAND OF THE HUMAN STOMACH, STAINED WITH HEMATOXYLIN AND EOSIN.

The conspicuous parietal cells stain red (Hardesty.)

The secreting portion, or *fundus*, of the gland is five to eight times as long as the duct or fovea, a fact which sharply differentiates the fundic from the pyloric glands of the stomach. The lumen of the secreting portion is so narrow as to be scarcely perceptible except by the use of special stains (precipitation technics) or high magnification

The fundus of the gland is lined by two distinct cell types, the chief and the parietal cells. The chief cells are relatively more abundant at the deeper portion

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man stomach secretes also a substance, the "intrinsic factor" which, acting upon an "extrinsic factor" derived from the food, produces a substance which prevents the development of pernicious anemia (Castle). This stomach extract, presumably a hemopoietic hormone, has been named "addisin" [16]

Pyloric Glands.—These are branched convoluted tubular glands with relatively long crypt-like ducts, into the bottom of which several secreting tubules open. According to Piersol, they occupy the pyloric fifth of the stomach.

The typical convolution is found only in the fundus of the gland, the course of the ducts being nearly straight. The branching, on the other hand, is chiefly confined to the ducts, which occupy the superficial two-thirds to three-fourths of the entire depth of the mucous membrane. In the pyloric mucosa, therefore, *three zones* may be distinguished: a superficial, middle and deep.

FIG. 343.   FIG 344.

FIG. 343—TRANSECTIONS OF THREE GLANDS OF THE FUNDUS REGION OF THE HUMAN STOMACH.

The section is taken from the portion of the glands near the lamina muscularis mucosae. The parietal cells are red, the central cells, black. Hematein and eosin. ×800.

FIG. 344—PORTION OF GASTRIC GLAND FROM THE FUNDUS REGION OF THE STOMACH.

L, lumen, ending in intracellular secretory canaliculi in the parietal cells (*P.c.*), C *c.*, chief cells Prepared by the Golgi chromate of silver impregnation method; highly magnified. (Zimmermann)

The *superficial zone* is narrow and contains the wide-mouthed foveolae which are lined with tall columnar cells similar to those of the fundic crypts.

The *middle zone* contains the narrowed portion of the ducts and is the broadest of the three zones. Several of the narrow ducts open into each foveola and further branching of the secreting tubules occurs to a limited extent. The epithelium of the ducts is of the low columnar variety, whose deeply stained basal

[16] Morris and Schiff, 1932.

gland where they are separated from the lumen by the chief cells they are ovoid or occasionally triangular in transection, the broad base of their triangular section being applied to the basement membrane, the wide-angled tip wedged between the bases of the adjacent chief cells. In the midportion of the secreting tubule the parietal cells approach nearer the lumen, and being inserted between the chief cells, they acquire an increased height and a pyramidal form. At the neck of the gland, where they present to the glandular lumens a broad surface, the parietal cells acquire a cuboidal shape. As the gland opens into its foveola the parietal cells, except for an occasional dislodged or misplaced individual, abruptly cease.
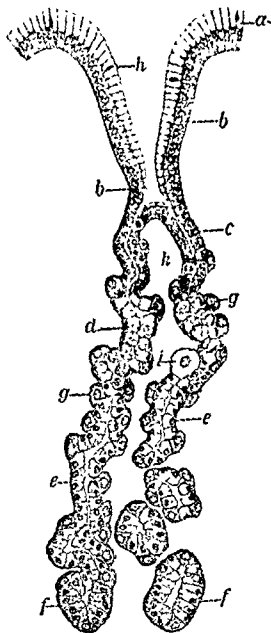
In those portions of the tubule where the parietal cells are more or less remote from the lumen they possess an extensive system of pericellular *secretory canals* which invest the cell in a basket-like manner and convey its secretion to the glandular lumen, where it mixes with the secretion of the chief cells. The parietal cells also possess a system of intracellular canaliculi.

The parietal cells are commonly believed to secrete the HCl of the gastric juice. But Harvey and Bensley [14] claim to have shown that free HCl is not present in these cells; their content is said to be chemically neutral or alkaline, and to consist largely of chlorides. The results of experiments with rabbits and various other vertebrates indicate that chlorine is secreted by the parietal cells in the form of a chloride of an organic base, and that the HCl is only set free after the secretion is poured out of the gland into the foveola. Hammett,[15] however, presents further evidence tending to show the presence of acid in the parietal cells. The normal hu-

FIG 342—FUNDIC GLAND OF STOMACH OF DOG

a, lining epithelium; *b*, crypt; *c*, neck of gland; *d*, transitional cells; *e*, chief cells; *f*, fundus of gland; *g*, parietal cells; *h*, leukocyte; *i*, giant parietal cell; *k*, mitosis (at right). (Ellenberger and v. Schumacher.)

14 Harvey, B. C. H. and R. R. Bensley, 1912.
15 Hammett, 1915.

man stomach secretes also a substance, the "intrinsic factor" which, acting upon an "extrinsic factor" derived from the food, produces a substance which prevents the development of pernicious anemia (Castle). This stomach extract, presumably a hemopoietic hormone, has been named "addisin." [16]

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[16] Morris and Schiff, 1932.

nuclei are spheroidal or ovoid, and are *progressively flattened as the secreting portion is approached.* The superficial cytoplasm of these cells stains readily with muchematein and often has a coarsely granular or reticular appearance.

The *deepest zone* contains the convoluted secreting portions and is *sharply marked off from the adjacent ducts,* since in a transection of the stomach wall its

tubules, owing to their convolution, are *nearly all cut across, while the ducts are* in longitudinal section. The clear stout columnar epithelium and broad lumen of *the fundus also contrast with the* slender finely granular epithelium and narrow lumen of the duct. It is this *narrow zone of peculiar convoluted tubules,* lying just within the muscularis mucosae, *by which the pyloric mucous membrane is most readily distinguished from all other regions of the alimentary canal.*

The tall columnar cells of the fundus possess a remarkably clear cytoplasm which reacts distinctly, though feebly, to *the specific stains for mucus.* The nuclei are flattened against the base of the cell and thus contrast sharply with the spheroidal nuclei of the ducts and crypts.

During secretion the cells become shrunken and their nuclei approach the center of the cell and become more nearly ovoid or spheroidal in shape.

There is no sharp line of demarcation between the fundic and the pyloric regions, the glands offering a gradual transition from the one type to the other.

Thus, in the human stomach, there is a broad transition zone which contains both fundic and pyloric glands. Indeed, in many individuals, parietal cells may be distributed throughout almost the entire gastric mucosa.

However, the transition from pyloric to duodenal mucosa is abrupt. This is correlated with a discontinuity as regards both the circular muscle layers and the submucous lymphatics. These structural conditions at the junction of stomach with intestine may explain the phenomenon of "pyloric block." [17]

Cardiac Glands.—A narrow region, about 5 millimeters in width, at the cardiac orifice of the human stomach contains glands whose form corresponds with that

of the fundic glands, though they are slightly more branched and are rather more tortuous, but which are lined by relatively clear columnar epithelium. Only occasionally are the chief and the parietal cells, which are characteristic of the
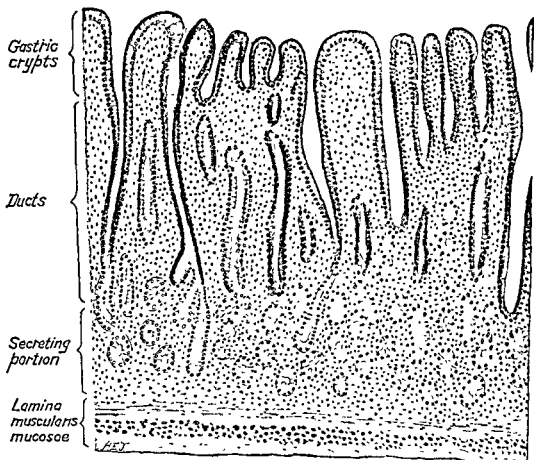
FIG 346.—TRANSVERSE SECTION OF THE TUNICA MUCOSA OF THE PYLORIC PORTION OF THE CAT'S STOMACH.

The glands are imbedded in the lamina propria mucosae, their deeper lying, convoluted, secreting portions staining less intensely in basic dyes. ×90

fundic glands, interspersed among the clear secreting cells of these tubules. The cardiac glands, therefore, appear to offer a transition from the esophageal to the more numerous fundic glands of the stomach. In certain mammals, e.g., the pig and the Marsupialia, the cardiac glands occupy a much larger area.

Corium.—The corium of the mucosa (lamina propria mucosae) consists of a delicate fibroreticular connective tissue which supports the blood and lymphatic vessels and is more or less infiltrated with lymphocytes. Hence in many portions it possesses the character of diffuse lymphoid tissue, though this tissue is characteristic of the interglandular rather than the interfoveolar portion of the lamina propria. In the latter situation, in sharp contrast to the intestinal villi with which the student may confound this region, the corium is decidedly fibrous and contains relatively few lymphocytes.

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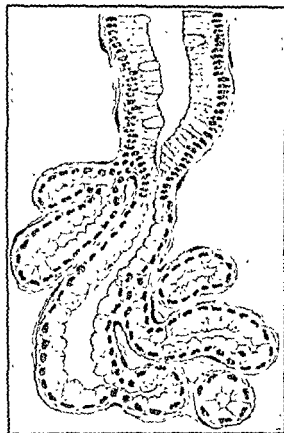
FIG 345—A PYLORIC GLAND, FROM SECTION OF HUMAN STOMACH, SHOWING DEEPER PORTION OF DUCT AND ASSOCIATED CONVOLUTED SECRETING FUNDI (Hardesty.)

tubules, owing to their convolution, are nearly all cut across, while the ducts are in longitudinal section. The clear stout columnar epithelium and broad lumen of the fundus also contrast with the slender finely granular epithelium and narrow lumen of the duct. It is this *narrow zone of peculiar convoluted tubules, lying just within the muscularis mucosae,* by which the pyloric mucous membrane is most readily distinguished from all other regions of the alimentary canal.

The tall columnar cells of the fundus possess a remarkably clear cytoplasm which reacts distinctly, though feebly, to *the specific stains for mucus.* The nuclei are flattened against the base of the cell and thus contrast sharply with the spheroidal nuclei of the ducts and crypts

During secretion the cells become shrunken and their nuclei approach the center of the cell and become more nearly ovoid or spheroidal in shape.

There is no sharp line of demarcation between the fundic and the pyloric regions, the glands offering a gradual transition from the one type to the other. Thus, in the human stomach, there is a broad transition zone which contains both fundic and pyloric glands. Indeed, in many individuals, parietal cells may be distributed throughout almost the entire gastric mucosa.

However, the transition from pyloric to duodenal mucosa is abrupt This is correlated with a discontinuity as regards both the circular muscle layers and the submucous lymphatics. These structural conditions at the junction of stomach with intestine may explain the phenomenon of "pyloric block." [17]

Cardiac Glands.—A narrow region, about 5 millimeters in width, at the cardiac orifice of the human stomach contains glands whose form corresponds with that

[17] Horton, 1928

submucosa. In the cardiac region they may lie very near the free surface of the mucosa.
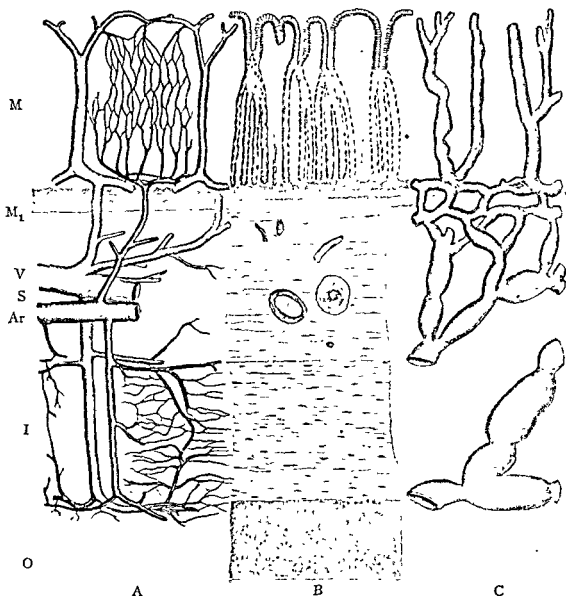
FIG. 348—BLOOD VESSELS AND LYMPHATICS OF STOMACH. (F. Mall.)

M, mucosa; *M₁,* muscularis mucosae, *S,* submucosa; *I* and *O,* circular and longitudinal muscles, *A,* blood vessels, *Ar,* artery; *V,* vein; *B,* microscopic anatomy; *C,* lymphatics. (From Szymonowicz-MacCallum, *Histology and Microscopic Anatomy.*)

Blood Supply.—The large blood vessels, derived from the branches of the celiac axis, enter through the subserous connective tissue of the omentum and form arches at the greater and lesser curvatures of the stomach.

From these arches, arteries lying in the subserous connective tissue are distributed to the ventral and dorsal surfaces of the gastric wall. These vessels supply branches which penetrate the muscular coat, giving off, on the way, arterioles to the intramuscular septum, and secondarily to the intramuscular capillary plexus,

FIG 347—TUNICA MUCOSA OF THE PYLORUS OF MAN WITH THE ADJACENT PORTION OF THE TELA SUBMUCOSA.

The mucosa contains a large solitary lymph nodule (lenticular gland). ×38.

In the deeper part of the mucosa occasional small lymph nodules, homologues of the solitary follicles of the intestine, are seen. These nodules (lenticular glands) lie just within the muscularis mucosae and do not, as a rule, penetrate into the

sections of its anastomosing branches. This latter plexus is much finer and contains smaller neurons than that of the muscular coat. Pericellular capsules are apparently lacking in these plexuses (Müller, Kuntz). The submucous plexus distributes its fibrils to the mucosa, where they terminate in and about the walls of the blood and lymphatic vessels, and to the epithelium of the secreting glands, where they end as varicose fibrils upon the cells. Kuntz [19] suggests that the ganglia

FIG 350—PROBABLE RELATIONSHIP OF SYMPATHETIC NEURONS IN MYENTERIC AND SUBMUCOUS PLEXUSES

Motor neurons, stippled, sensory neurons, solid *1*, lamina propria mucosae; *2*, lamina muscularis mucosae , *3*, tela submucosa; *4*, tunica muscularis; *M*, myenteric plexus; *S*, submucous plexus, *a*, axons, *d*, dendrons (Kuntz)

of the myenteric and submucous plexuses include both motor and sensory neurons, and that the fibers which terminate on cells of the digestive epithelium are the dendrons of sensory cells.

SMALL INTESTINE

The small intestine constitutes the longest portion of the digestive tube. It connects the pylorus with the colon It measures about 7½ meters (24 feet) in length It may be divided into three segments: (1) the duodenum, about 11 inches in length; (2) the jejunum, including the upper two-fifths, about 9 feet, and (3)

[19] Kuntz, 1913

and spread out in the areolar tissue of the submucosa in which they form an extensive arterial plexus. Branches from this submucous plexus enter the mucous membrane and form a dense capillary plexus whose elongated meshes inclose the secreting glands.

Near the surface of the mucosa these vessels enter a plexus of small venules which, by union, form larger branches and convey the blood outward to a venous plexus at the outer border of the mucosa, whence it returns to the larger veins of the submucosa. These veins, after receiving venules from the muscular coat, pass outward to the subserous connective tissue in company with the entering arteries and finally reach the gastric, splenic and portal veins.

Lymphatics.—The lymphatics arise by vascular loops or dilated extremities between the secreting glands of the mucosa. At the outer border of the mucous membrane they form a delicate anastomosing plexus from which branches penetrate the muscularis mucosae and enter a broad submucous plexus whose efferent vessels pierce the muscular coat on their way to lymph nodes which are situated in the folds of the omentum at either

FIG. 349.—TERMINATION OF SYMPA-
THETIC NERVE FIBERS.

A, on smooth muscle cell; *B*, on cells of the digestive epithelium, ileum of cat; *C*, on cells of the digestive epithelium, stomach of cat; *D*, on parietal cell, stomach of cat. (Kuntz)

curvature of the stomach.

According to Horton [18] there is no demonstrable continuity between the submucous lymphatics of the stomach and those of the duodenum. The lymphatic drainage of the stomach is said to be represented by four distinct areas. The largest of these is the area drained by the lymph nodes along the lesser curvature. The second most important is that in the greater curvature, draining into the inferior gastric and subpyloric groups of lymph nodes. The third drains towards the splenic group of nodes, and the fourth drains the distal portion of the pars pylorica to lymph nodes above the pancreas.

Nerves.—The nerves of the stomach are derived from sympathetic trunks, the splanchnic nerves, and from the vagi. The vagi are believed to be chiefly excitatory, the splanchnics inhibitory in function. The nerves enter with the blood vessels and pierce the muscular coat. They connect with two plexuses of anastomosing nerve trunks. the myenteric (Auerbach's), in the intramuscular fibrous septum, which contains ganglionic enlargements at many of its intersections and distributes its fibrils to the smooth muscle; the submucous (Meissner's), lying in the deeper part of the submucosa, which also contains small ganglia at the inter-

18 Horton, 1928

sections of its anastomosing branches. This latter plexus is much finer and con-
tains smaller neurons than that of the muscular coat. Pericellular capsules are
apparently lacking in these plexuses (Müller, Kuntz). The submucous plexus
distributes its fibrils to the mucosa, where they terminate in and about the walls
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[19] Kuntz, 1913

the ileum, including the lower three-fifths, about 14 feet, of the remainder. The duodenum lacks a mesentery, it is only partially enveloped by a serosa, and it has the greatest diameter, about 47 millimeters (2 inches). Below the duodenum the caliber of the small intestine gradually decreases until a diameter of 27 milli-

meters (a little over 1 inch) is attained, at the end of the ileum. The three portions differ also in the shape and number of villi, and in other histologic details which will be described below. The inner surface is modeled by a succession of tall circular folds, the *valvulae conniventes* or *plicae circulares*, involving the submucous layer. These plicae become less closely spaced throughout the lower portion of the ileum and generally disappear toward its end. They serve to increase the absorbent surface of the intestinal mucosa, and unlike the villi, which are scattered over their surface, they are not subject to variations dependent upon altering degrees of distention.

FIG. 351 —SECTION THROUGH THE COMMENCEMENT OF THE DUODENUM AT THE PYLORUS. (Klein)

v, villi; *b*, apex of a lymphoid nodule; *c*, crypts of Lieberkuhn; *m*, muscularis mucosae; *s*, secreting tubes of Brunner's glands; *d*, ducts of pyloric glands of stomach; *g*, tubes of these glands cut across in mucous membrane; *t*, deep-lying tubes situated in submucous tissue, and corresponding with Brunner's glands of the intestine. (From Quain, *Anatomy*.)

The structure of the serous coat of the small intestine is identical with that of the stomach. The muscular coat consists of an inner and an outer layer of unstriped muscle fibers which are separated by a thin connective tissue septum. The inner circular layer is much thicker than the outer longitudinal.

The regular disposition of the muscle fibers as an outer longitudinal and an inner circular layer serves as a guide to the recognition of the direction in which a given microscopical section has been cut. In transections of the intestine the muscle fibers of the outer layer of the muscular coat are transversely cut; in longitudinal sections of the organ the same fibers are seen in longitudinal section.

Submucosa.—The tela submucosa of areolar connective tissue is identical with that of the stomach except in the duodenum where it is penetrated by the branched tubulo-acinose mucous *duodenal* (Brunner's) *glands*. The lamina muscularis mucosae forms a complete muscular layer and, except in the duodenum, is not penetrated by the glands.

More accurately both the tela submucosa and the tunica muscularis consist

of fibers spirally arranged in the manner of a left-handed helix. Carey [20] describes the tela submucosa as composed of two sets of fibrils, the inner wound closely, making one complete turn in every 0 5 to 1 millimeter; the outer more elongated, making one turn in every 4 to 10 millimeters. Similarly, the inner layer of the tunica muscularis consists of spirally disposed fibers making one turn every 0 5 to 1 millimeter; the fibers of the outer layer one complete turn every 200 to 500 millimeters. Peristalsis finds its explanation in the reciprocal elongating action of the outer loose muscle spiral and the inner close spiral respectively.

Mucous Membrane.—The mucous membrane (tunica mucosa) of the small intestine is divisible into an inner and an outer zone. In the inner zone the corium forms finger-like projections, the intestinal *villi*, which are covered with tall columnar epithelium containing many mucus-secreting goblet cells. The villi are characteristic of the small intestine, in which alone they occur. They serve to increase the area of the lining epithelium of the intestine, whose chief function is that of absorption.

The outer zone of the mucous membrane includes all that portion between the muscularis mucosae and the bases of the intestinal villi. It is almost completely occupied by the simple tubular *intestinal glands* (or crypts of Lieberkühn).

Corium.—The corium (lamina propria) of the small intestine, in which the intestinal glands are embedded, and which forms the substance of the intestinal villi, consists of a fibroreticular stroma which is so infiltrated with lymphocytes as to form a diffuse lymphoid tissue. In many parts of the mucosa the lymphoid tissue forms isolated nodules, the *solitary nodules*, or aggregations of such nodules, which are known as the *agminate nodules* or *Peyer's patches*. Solitary nodules occur throughout both the large and the small intestine. Peyer's patches are found only in the small intestine and are most numerous in the upper portion of the ileum.

STRUCTURE OF THE SOLITARY NODULES.—The structure of the solitary nodules does not differ from that of other lymph nodules. They vary much in size, most of them being of sufficient diameter to occupy the entire thickness of the mucous membrane. They push aside the adjacent intestinal glands by which they are encircled, and few or no villi project from their free surface. The adjacent villi are so inclined that their free ends often hide all but the projecting apex of the ovoid solitary nodule.

The largest of the solitary nodules not only produce a distinct elevation of the surface of the mucous membrane but may even break through the muscularis mucosae and project into the connective tissue of the submucosa. The solitary nodules, like other lymph nodules, usually contain a germinal center.

AGMINATE NODULES (AGGREGATE NODULES, PEYER'S PATCHES).—Agminate nodules are formed by accumulations of lymph nodules, usually occurring in that portion of the intestinal mucosa which is farthest removed from the attachment of the mesentery They frequently form oval areas of macroscopic size. They

[20] Carey, 1921

usually number about thirty, though there may be fewer, and frequently many
more. The number of their constituent nodules is variable, frequently they contain
as many as fifteen or twenty. Each of these nodules is usually invested by a thin
fibrous capsule, though frequently they are confluent with one another.

Fig 352.—From a Longitudinal Section through the Duodenum of a Cat. ×34
(From Szymonowicz-MacCallum, *Histology and Microscopic Anatomy*)

The long axes of the ovoid nodules exceed the average thickness of the
mucous membrane so that the patch forms a superficial elevation of the mucosa
and its deeper surface penetrates the muscularis mucosae and enters the sub-
mucous coat. Hence occasional fragments of the muscularis mucosae often occur

between the bases of the constituent nodules. Villi are found upon the free surface of the agminate nodules only in the intervals between the constituent units. The largest of the nodules lie near the center of the patch, the smallest are found at its periphery. The agminate nodules become the chief seats of infection in typhoid fever.

FIG. 353—THE CENTRAL PORTION OF A PEYER'S PATCH IN THE ILEUM OF A DOG'S INTESTINE.

a, villi; *b*, glands, *c*, lymph nodules, an agminated follicle; *d*, connective tissue of the submucosa; *e*, a portion of the muscular coat. Hematein and eosin Photo. ×35

Above the level of the ileum the largest collections of lymphoid tissue in the intestinal mucosa occur in the upper part of the duodenum, where there are extensive infiltrations of dense lymphoid tissue, many of which contain typical nodules with germinal centers. These masses of lymphoid tissue are penetrated by the ducts of the duodenal glands, whose secreting portions form a bed upon which the lymphoid tissue rests. The duodenal patches differ slightly from those in the ileum in that they form a more confluent mass with relatively fewer nodules; they

also possess a more diffuse character, are more deeply situated, and are therefore covered by the corium of the mucosa which contains both intestinal glands and villi.

Intestinal Villi.—The intestinal villi are long finger-like projections (from 0.5 to 1 millimeter in length) which vary much in form in different mammals and in different portions of the canal in the same individual. They are perhaps most highly developed in the dog, where they form long projections with expanded or clubbed extremities and a constricted base or neck.

In man the villi are of a more conical shape, the base being, as a rule, slightly broader than the free extremity. In the duodenum of man they possess a foliate shape, in the jejunum they are conical or somewhat clavate, in the ileum they are generaly filiform. The villi are most abundant in the duodenum and the jejunum (24 to 40 per square millimeter) and less numerous in the ileum (15 to 30 per square millimeter) .(Piersol). According to Johnson [21] they are more or less variable structures, their shape and height changing with the degree of distention of the tube.

The villus is formed by a projection of the corium which is covered by the lining epithelium of the intestine. The axis of the villus contains a large lymphatic capillary or *lacteal*, which begins in the inner third and proceeds outward through the corium to enter a lymphatic plexus lying just within the muscularis mucosae An occasional villus may contain several lacteals. In the base or outer portion of the villus the lacteal is surrounded by small groups of smooth muscle fibers which are disposed in an axial direction, and which are ontogenetically derived from the muscularis mucosae. Many of these fibers turn outward and are attached to the basement membrane beneath the epithelium at the sides and tip of the villus. By their rhythmic contraction the muscle fibers of the villus aid in expelling the contents of the lacteal.

The body of the villus consists of diffuse lymphoid tissue having a reticular stroma in which the lacteal, the muscle fibers, and the blood vessels are embedded.

Each villus is supplied with one or more arterioles which enter at the base and pass to the inner third, where they form an abundant plexus of from 15 to 20 capillaries about the blind extremity of the lacteal and in the apex of the villus. Here they are adherent to the bases of the epithelial cells. The surface of this capillary plexus is estimated at about 80 per cent of that of the epithelium. Minute venules collect the blood from this plexus, and following the course of the lacteal,

FIG. 354.—LONGITUDINAL SECTION OF VILLUS.

G, goblet cell; L, lacteal; s, striated border of columnar cell.

21 Johnson, 1913

make their exit from the base of the villus to join the venous plexus in the deeper part of the mucosa (Fig. 357).

LINING EPITHELIUM.—The lining epithelium of the intestine, which also clothes the villi, rests upon a distinct reticular basement membrane and consists of columnar and goblet cells. The large number and peculiar appearance of the goblet cells is highly characteristic of this tissue.

The columnar cells are peculiar in that they possess a characteristic striated cuticular border when examined under moderately high magnification. They possess a finely reticulated cytoplasm and an ovoid nucleus which is situated at the proximal end or base of the cell. Frequently the cytoplasm contains droplets of fat which are in process of absorption. Occasional leukocytes find their way into the epithelial coat, whence they may penetrate the intercellular substance and enter the intestinal canal.

Intestinal Glands (Glands of Lieberkuhn, Mucous Crypts).—The intestinal glands occur throughout the entire extent of the small and large intestines, including the cecum and the appendix. They are simple tubules which extend the whole depth of the mucous membrane and in the small intestine open upon the free surface between the bases of the villi. Hence the lining epithelium of the glands becomes continuous with that which clothes the villi. The glands are imbedded in the diffuse lymphoid tissue of the corium; they rarely branch. They consist of a lining epithelium and a basement membrane.

The *epithelium* of the glands contains three types of cells: *columnar cells, goblet cells* and the *granule cells* of Paneth. The columnar and goblet cells resemble those which clothe the villi. The columnar cells which line the neck of the glands, however, possess only a very indistinct cuticular border and such border is entirely lacking in the fundus cells of the glands. The epithelium of the glands appears to take no part in the process of absorption and therefore contains no fat globules. It secretes a mucous fluid.

At the neck of the gland the epithelium frequently contains mitotic figures which have been demonstrated in man as well as in the lower mammals. Little or no mitosis has been demonstrated in the fundus of the gland or upon the free surface of the villi. On these facts the so-called *wander theory* of Bizzozero is founded According to this theory there exist in the neck of the glands certain indifferent cells which are capable of reproduction by mitosis and whose daughter cells move toward the free surface, being at the same time differentiated into either the goblet or the columnar cells of the villi.

Bizzozero originally considered that the granule cells of Paneth at the fundus of the glands were intermediate phases in the formation of goblet cells. However, as there is little or no mitosis in the region where these peculiar cells occur and as the granule cells are never displaced toward the surface, it seems more probable that, as also in the gastric glands, the indifferent genetic cells of the neck of the tubule develop on the one hand the superficial goblet and columnar cells which clothe the villi, and on the other hand, the true secreting cells in the fundus of the intestinal glands.

The *granule cells of Paneth* [22] are confined to the extreme tip or blind extremity of the fundus of the glands. They are pyramidal or low columnar cells whose spheroidal nucleus is situated close to the basement membrane. Their cytoplasm presents a delicate reticulum which is filled with coarse granules which in some cells are of a basophil nature.[23] Generally they contain still coarser granules which are strongly eosinophil. The exact function of these peculiar cells is unknown, but that they are true secreting cells seems highly probable. Miram [24] made a careful study
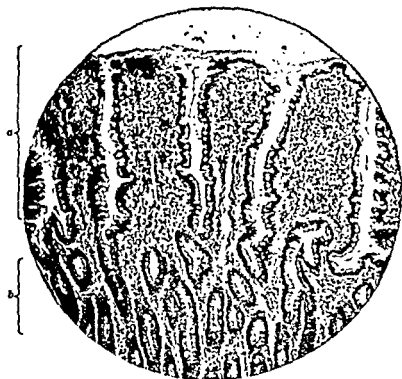
FIG. 355.—SEVERAL VILLI FROM THE SMALL INTESTINE OF THE DOG, IN LONGITUDINAL SECTION. *a*, villi; *b*, crypts of Lieberkühn. Hematein and eosin. Photo ×185.

of these cells in the small intestine of the mouse. He maintains that they are important in the young for the digestion of milk, perhaps by secreting a fat-splitting enzyme; and throughout life for the absorption of fat, perhaps also of albuminoid material.

Still other types of granular cells of unknown significance have been described by Kull [25] in the fundus of the intestinal glands, and among the epithelial cells clothing the villi: (1) acidophil cells, with the basal oxyphilic granules finer than those of the Paneth cells; and (2) chromaffin cells with yellowish basal granules, coarser than those of the acidophil cells and finer than those of the cells of Paneth

[22] Paneth, 1888.
[23] Klein, 1906.
[24] Miram, 1912.
[25] Kull, 1913.

These three types of cells are present in man and certain vertebrates; they are said to have no genetic relationship. The chromaffin cells of the intestinal epithelium were first recognized by Schmidt,[26] who designated them as yellow cells.* Ciacco [27] reports similar cells also in the duodenal (Brunner's) glands. Champy [28] has also described mitochondria in the cells of the intestinal glands.

The intestinal glands are confined to the narrow deeper zone of the intestinal mucous membrane. Their lumen, after fixation, contains only the coarsely reticular mucous secretion.

The student should be warned to distinguish carefully between the transverse sections of the tubular glands which are confined to the *deep* zone of the mucous membrane and the similar sections of the villi which are only found in the *superficial zone* and whose epithelial coat, instead of inclosing a mere reticular mass of mucous secretion invests an organized body of diffuse lymphoid tissue.

Duodenal (Brunner's) Glands.—The duodenal glands of Brunner are tubulo-acinose glands which furnish a muco-albuminous secretion. They appear to represent the continuation into the intestine of the pyloric glands of the stomach, and they occur in decreasing proportion throughout the entire length of the duodenum. Around the duodenal papillae, however, they become locally more numerous. They are sharply distinguished from the pyloric glands by their larger size. Moreover, the secreting portion of the duodenal glands is only found in the submucosa and the deeper part of the mucous membrane, where the secreting acini form very numerous groups, the tubules of each of which are connected with the terminal subdivision of a duct.

FIG. 356—RECONSTRUCTION MODEL OF A BRUNNER'S GLAND, FROM THE HUMAN DUODENUM

Three partially blended ducts pass into the submucosa and end in expanded alveoli ×344 (Maziarski)

The ducts of the duodenal glands open on the free surface between the villi by means of crypt-like tubules which are lined by tall columnar epithelium and can only with difficulty be distinguished from the adjacent intestinal glands. In the deeper part of the mucous membrane the ducts branch and pursue a somewhat tortuous course to the fundus of the gland. At the fundus it is found that the terminal acini of each subdivision of a duct are invested with a distinct fibrous capsule.

The secreting epithelium of the duodenal glands consists of tall columnar cells which surround a wide lumen. When loaded with secretion the cells are swollen

[26] Schmidt, 1905   [27] Ciacco, 1907.   [28] Champy, 1909
* Also designated argentaffine cells because of a marked capacity of their granules to reduce silver salts They may become the site of "argentaffine carcinomas." (Willis, R. A., 1940, Med. J., Australia, 2 395).

and clear, but become shrunken and granular after a period of activity. Their cytoplasm reacts to the specific stains for mucin only when these are applied for a considerable time in concentrated solution. The spheroidal nucleus is situated at the proximal or basal end, and as the cell fills with secretion the nucleus becomes progressively flattened.

Blood Supply.—The blood supply of the small intestine resembles that of the stomach. The branches of the mesenteric arteries pass around the intestinal wall in the subserous connective tissue. From this point they penetrate the muscular coat to

Fig. 357—THE BLOOD VESSELS OF THE SMALL INTESTINE OF A DOG, DRAWN AFTER AN INJECTED PREPARATION.

The arteries are striped, the veins black, the capillaries open. *A*, villi; *B*, glands, *C*, muscularis mucosae; *D*, submucosa, *E*, circular, and *F*, longitudinal layer of the muscular coat. *a*, venule beginning from the capillaries of the villus, and at *b*, from those among the glands, *c*, artery to the villus, *d*, venules in the deeper part of the mucosa; *e*, main arterial trunk to several adjacent villi, *f*, arterial branch to the glandular region. Highly magnified. (After Mall, from Oppel.)
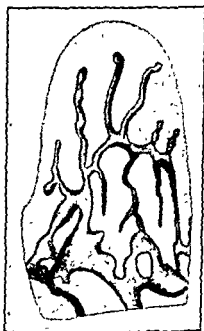
FIG 358—INTESTINAL VILLUS OF RAT, SHOWING LACTEALS INJECTED WITH BERLIN BLUE.

(Ranvier.)

form intramuscular and submucous plexuses. From the latter a few branches supply the adjacent portion of the inner layer of the muscular coat, but most of them pass to the mucous membrane, in which a plexus lies just within the muscularis mucosae and distributes its branches to the capillaries about the intestinal glands and to the intestinal villi.

The artery of the villus enters at its base, and distributing capillaries along its course, forms in the distal part of the villus an abundant capillary network from which efferent venules return by a similar course. The artery, however, is found near the axis, the venules near the periphery of the villus.

Branches from the submucous and mucous arterial plexuses also supply capillaries to the duodenal glands in the duodenum as well as to the solitary and agminated lymph nodules. About each of the lymph nodules they form circular anastomoses, from which radial capillaries are distributed within the nodule.

The veins pursue a course similar to that of the arteries. On their way to the mesenteric vessels they form mucous, submucous, intramuscular, and subserous plexuses, and drain into the portal system. The portal vein and its main tributaries lack valves. Valves are present only in the smaller tributaries, beginning in the tunica muscularis throughout the digestive tube and prevailing generally in the mesenteric veins.

Lymphatics.—The lymphatics or *lacteals* of the small intestine begin in the distal part of the villi as lymphatic capillaries, each having, as a rule, a pouched, blind extremity During the digestion of fats they become distended with a whitish fatty lymph called *chyle*. At their origin the lacteals are frequently branched, or they may even form a scanty anastomosis. They finally unite to form a central lacteal in the axis of the villus, which empties into a rich plexus about the intestinal glands, or like the efferent vessels of this plexus, they may pass directly to the larger lymphatic vessels of the submucosa.

From the submucous plexus numerous efferent lymphatic vessels penetrate the muscular coat, receiving the lymph from the vessels of the intramuscular septum. They empty into the larger lacteal vessels of the mesentery which are intimately connected with numerous mesenteric lymph nodes. In the mucosa and submucosa the lacteals from sinuses which surround the bases of the solitary and agminated nodules Thus, much of the chyle is permitted to come into relation with the parenchyma of these organs before leaving the intestinal mucosa.

The group of mesenteric lymph nodes generally includes one of relatively large size. The mesenteric lymphatics converge on this node. Because of its remarkable size it has been specially named the "glandula mesenterica magna," or "pancreas of Aselli"

Nerve Supply.—The nerve supply of the intestine is similar to that of the stomach. The unmyelinated fibers form an intramuscular *myenteric ganglionic plexus* (Auerbach's) for the supply of the muscular coat, and a *submucous plexus* (Meissner's) which supplies branches to the blood vessels and to the glands of the mucosa The finer branches in the mucous membrane penetrate to the villi, forming a delicate plexus of naked fibrils about its blood vessels and lacteals, and upon its epithelium.

Intestinal Absorption.—The absorption of fat consists essentially of *three phases·* its absorption into the intestinal epithelium, its secretion into the lymphoid tissue of the villus and its entrance into the lacteal vessels. In an animal killed during the absorption of fat, the intestinal villi, after fixation by solutions of

osmium tetroxide, contain fat in the epithelium, the lymphoid tissue and the central lacteal.

In the epithelium, fat is contained in the form of fine droplets which are most numerous in the distal or free ends of the cells. They are also found in the intercellular spaces. During absorption the epithelial cells of the villi become much swollen and elongated. As the process subsides they return to their former size, and become relatively shrunken. When most distended the intracellular fat droplets are the most abundant; as the cells shrink the intercellular droplets increase relatively in number.[29] The relative size of the epithelial cells and the abundance of intra-epithelial fat is apparently dependent upon the activity of the processes of absorption.

FIG. 359—APEX OF AN INTESTINAL VILLUS OF A RABBIT WHICH HAD BEEN FED WITH MILK.

The fat droplets have been blackened by fixation with picric acid and osmium tetroxide The figure shows the distribution of fat during certain stages of absorption Alum carmine stain Highly magnified (After R. Heidenhain, from Oppel.)

As to the manner in which the fat enters the epithelium there is some doubt. Schäfer[30] suggested that the leukocytes by their ameboid activity inclose the emulsified droplets in the intestinal lumen and convey them into the substance of the villi. It seems more probable that the fats are saponified in the intestinal tract, and enter the epithelium in solution.[31] Here they are again synthesized into neutral fat by the activity of the epithelium.[32] Such a process accounts for the abundance of fat within the distal portions of the cells. The droplets are then secreted into the intercellular and subjacent tissue spaces.

The second phase of absorption includes the transference of the fat particles to the lacteal. This process appears to depend partially, at least, upon the activity of the leukocytes (monocytes) as suggested by Schafer, the particles of fat thus finding their way through the diffuse lymphoid tissue. According to Reuter,[33] fat droplets are found in the tissue spaces as well as in the lymph corpuscles of the diffuse lymphoid tissue, a fact which would seem to indicate that other agencies aid in the transit of the fat from the epithelium to the lacteal than are accounted for by the purely mechanical theory of Schafer.

The third phase includes the secretion of the fat into the lumen of the lacteal; this is, at least partially, accomplished by the disintegration of fat-laden leuko-

[29] Drago, 1900
[30] Schäfer, 1885.
[31] Whitehead, 1909
[32] Pflüger, 1900.
[33] Reuter, 1902

cytes which, by ameboid motion, have found their way into the lacteal. Other fat particles may possibly find their way into the lacteal without the aid of the leukocytes—a process which may be more or less dependent upon the vital properties of the lining endothelium.

The absorbed fat enters the blood stream via the thoracic and right lymphatic ducts. It is transformed into lecithin by the liver and stored in small part in the membrane of the erythroplastids. Most of the fat absorbed from the intestine reaches the tissues in the form of minute particles (chylomicrons) and is "removed and stored as fat by a process of which the details are unknown."[34] Carbohydrates pass directly through the gastro-intestinal epithelium to the blood capillaries. Similarly, the digested proteids enter the blood stream directly as amino-acids.

In about 2 per cent of all individuals there occurs, attached to the ileum at a level approximately 32 inches above the ileocecal valve, a pouch-like appendix known as *Meckel's diverticulum*. It constitutes an anomaly, the result of the persistence of the proximal portion of the embryonic yolk stalk; it varies in length from 1 to 3 inches; its distal end may be free or attached to either mesentery or body wall. The wall consists of the usual four coats of the small intestine. The mucosa generally includes villi and intestinal glands, resembling the mucosa of the ileum. In approximately 15 per cent of these diverticula the mucosa is of the gastric type, more generally of the fundic variety. This type of mucosa is frequently associated with a peptic ulcer of the diverticulum. In rare instances the mucosa resembles that of the colon, or may even include pancreatic tissue.

THE LARGE INTESTINE

The large intestine includes the cecum, with the attached vermiform appendix, the colon (ascending, transverse and descending portions) and the rectum. It measures about 180 centimeters (5 feet) in length, and from 3 inches at the beginning to about 1½ inches towards the end of the colon. It connects the ileum with the anus. The vermiform appendix represents an atrophic vestige of the terminal portion of the embryonic cecum.

The three outer coats of this portion of the alimentary canal are identical in structure with those of the small intestine, with a single exception in the irregular distribution of the outer layer of the muscular coat, which in the large intestine forms three distinct longitudinal bands or thickenings, the *teniae (lineae) coli*. At other parts of the circumference of the organ the outer muscular layer is slightly thinner than in the small intestine. In certain mammals, *e.g.*, cat and cow, the longitudinal muscle layer forms a coat of uniform thickness. The colon of the horse has four teniae, that of the pig only two.

Since the teniae are shorter than the other coats of the colon, they produce a succession of *sacculations* or *haustra* the boundaries of which are marked internally by crescentic folds, involving the entire wall, the *plicae semilunares*. These sacculations furnish conspicuous external marks by which the large can be differentiated macroscopically from the small intestine. Another differential characteristic of the colon is the presence generally of fringes and bags of adipose tissue attached along the median border to the serosa, the *appendices epiploicae*.

Mucous Membrane.—The mucous membrane of the large intestine may be best described by comparison with that of the small intestine. If the mucosa of the latter organ be considered to contain two zones, a superficial layer of villi and a deeper glandular layer, that of the large intestine may be said to consist of only the deeper of these zones. It therefore possesses no villi, and its simple somewhat longer (about 0.5 millimeter) tubular glands extend from the free surface almost to the muscularis mucosae. Villi are present, however, in the embryo, but disappear about the sixth month.[25]
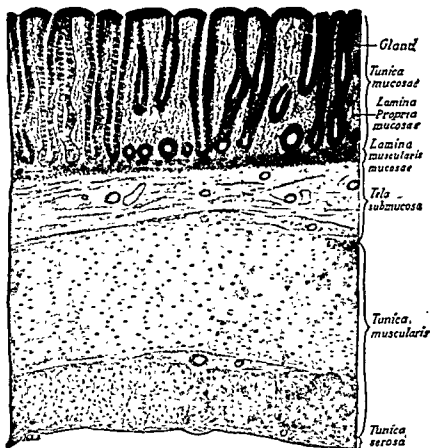
FIG 360—TRANSVERSE SECTION OF COLON OF DOG.
The majority of the glands are cut longitudinally, some transversely, a few obliquely. ×45

Lining Epithelium.—The lining epithelium of the large intestine is of the simple columnar variety and has only an indistinct cuticular margin. That of the glands contains both columnar and goblet cells, the latter being far more numerous than in the small intestine. The large intestine contains no plicae circulares.

Lymphoid Tissue.—The lymphoid tissue of the large intestine occurs in the corium in diffuse form, and as solitary nodules, which latter frequently break through the muscularis mucosae and protrude into the submucosa. Lymph nodules

25 Johnson, 1913

are especially abundant in the rectum and in the *vermiform appendix*. In the latter the nodules are more or less confluent, a condition which is not found elsewhere in the large intestine. In the appendix the greater portion of the mucous membrane is invaded by lymphoid tissue, and the glands are much diminished in both number and size. (Fig. 361).

Vascular and Nerve Supply.—The vascular and nerve supply of the large intestine is identical in its arrangement with that of the small intestine. The mucous membrane contains a capillary plexus of blood and lymphatic vessels in the corium about the glands. The nerves of the large intestine include both myelinated and unmyelinated fibers. The latter supply its muscular coats and blood vessels. The former end in naked varicose or knobbed fibrils beneath and upon the

FIG. 361.—TRANSECTION OF THE VERMIFORM APPENDIX OF MAN.

The tela submucosa contains three lymph nodules (at the right), two of which have pushed beyond the scattered bundles of the lamina muscularis mucosae into the lamina propria of the tunica mucosa, a mass of diffuse lymphoid tissue (at the left), and some adipose tissue. ×11.

epithelium of the glands. The usual myenteric (Auerbach's) and submucous (Meissner's) plexuses appear in the large intestine with the same structure and location as elsewhere in the alimentary canal.

In the *rectum* the lining epithelium is continuous at the anus with the stratified squamous epithelium of the skin. In this region also, the circular fibers of the inner layer of the muscular coat are much thickened to form the internal rectal sphincter. Lymphoid tissue abounds in the rectal mucous membrane. The glands are less numerous but larger than in the colon proper, and the mucosa is thicker. In the lower portion of the rectum the mucosa is thrown into a number of longitudinal folds, the *rectal columns*, at which level the columnar epithelium changes

to stratified squamous type. At about the middle third of the anal canal occurs a smooth, glistening annular area, the so-called "pecten."

Ileocecal (Colic) Valve.—The ileocecal valve, which guards the orifice by which the small intestine opens into the large, is formed by a reduplication of the mucous membrane, which is strengthened by a thickening and overlapping of the circular muscular layers of both small and large intestines. The valve itself consists of an upper and lower segment enfolding the slit-like orifice; laterally the two folds unite to form the frenulum, which encircles the colon and marks the boundary between it and the cecum.

The outer longitudinal muscular layer is continued directly from the wall of the ileum to that of the *cecum*, and therefore pursues a relatively shorter course than either the internal muscular layer or the mucous membrane. Section of only the outer layer of the muscular coat permits one to straighten the fold of the intestinal wall and thus obliterate the valve. In other words, the outer muscular layer is not included in the valvular duplication.

The *lamina muscularis mucosae* is slightly thickened at the margin of the valve. At this point also, the villi become shorter and at the margin of the cecal surface of the valve they entirely disappear.

The tabular statement on page 365 of the more important characteristics of the several portions of the alimentary canal may be of assistance to the student in the identification of microscopic sections of these organs.

THE SALIVARY GLANDS

The salivary or oral glands include the smaller glands of the oral cavity and three pairs of large compound tubulo-acinose glands, the parotid, submaxillary and sublingual glands. The three large pairs are commonly designated as the salivary glands proper, the smaller as the accessory salivary glands. All these are of the tubulo-acinose type, but certain ones secrete a mucous fluid while others produce an albuminous secretion which contains no mucus. The former are known collectively as the *mucous*, the latter as the *serous* salivary glands. Still other salivary glands secrete a fluid which is intermediate in composition, and as these glands contain certain alveoli which resemble those of the mucous, and others which are somewhat similar to those of the serous glands, this type is known as *mixed* salivary glands.

The salivary glands may therefore be subdivided into: (1) mucous glands; glands on the anterior surface of the hard and soft palate (*palatine glands*) and the mucous glands of the margins and root of the tongue; (2) mixed glands; submaxillary, sublingual, molar, buccal, labial and the anterior lingual glands (of Nuhn); (3) serous glands · parotid, and von Ebner's glands at the base of the tongue.

The form of the salivary glands will be appreciated by examination of the accompanying diagram (Fig 362) which represents one of the smaller glands of

TABLE I

	Esophagus	Cardiac Stomach	Fundus Stomach	Pyloric Stomach	Duodenum	Ileum and Jejunum	Large Intestine
Lining epithelium ..	Stratified squamous	Columnar	Columnar	Columnar	Columnar and goblet	Columnar and goblet	Columnar and many goblet
Glandular epithelium...	Columnar, mucous	Muco-albuminous, few parietal cells	Serous, chief and parietal cells	Columnar, muco-albuminous	Columnar, muco-albuminous	Columnar and goblet	Columnar and very many goblet
Glands.. { Type......	Branched tubulo-acinose	Branched tubular	Branched tubular	Convoluted tubular	Simple tubular and branched tubulo-acinose	Simple tubular	Simple tubular
Situation...	Mucosa and submucosa	Mucosa	Mucosa	Mucosa	Mucosa and submucosa	Mucosa	Mucosa
Lymph nodules........	Rare, small	Many, medium	Few, small	Few, small	Many, large, confluent	Solitary and agminated	Many, large, solitary
Muscular coat........	Striated or smooth	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth
Villi	None	None	None	None	Present	Present	None

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this type. The larger ones are constructed in the same manner, the larger number of their secreting alveoli or acini arising through a more complex duct system.

The larger ducts of the gland are lined with columnar cells, which, as they approach their termination, become superposed and thus offer a gradual transition to the stratified squamous epithelium upon whose surface they open. The epithelium rests upon a basement membrane which, in the larger ducts, is invested with a fibro-elastic coat containing a few longitudinal smooth muscle fibers.

The ducts divide and subdivide in an arborescent manner, the larger branches lying in the connective tissue which invests the lobules into which the gland is subdivided, while the smaller branches are found within the lobule. The duct system is thus divisible into interlobular and intralobular ducts; the latter include generally an *excretory* portion continuous with the interlobular duct, a modified *salivary secretory* portion, and a constricted *intercalary* or *intermediate* portion connecting with the acinus.

FIG 362.— A SMALL MUCOUS GLAND FROM THE ORAL MUCOSA OF A RABBIT

a, mucous alveoli; *e*, epithelium of the oral mucosa; *m*, mouth of the glandular duct ×70 (Kolliker.)

In the smaller glands of the mouth the number of subdivisions of the duct system is relatively small, but in the larger salivary glands the small ducts are practically innumerable. Thus, in the submaxillary gland, Flint[38] found that the interlobular duct system formed 1500 terminal branches, each of which entered a lobule and was further subdivided into intralobular and intercalary ducts before terminating in the secreting acini. The larger glands may therefore be said to bear to the smaller ones represented in Figure 362, a relation which is comparable with that of a full-grown tree to the youngest sapling.

The larger salivary glands are enveloped by a fibro-elastic capsule continuous with the adjacent areolar tissue. From this capsule coarse trabeculae enter to divide the gland into groups of lobules, the lobes. The lobules are invested by more delicate septa from the interlobar trabeculae. The ducts of the interlobar connective tissue may be designated *interlobar ducts* to distinguish them from the *interlobular ducts* between the lobules. These are the *excretory* ducts of the gland; the salivary intralobular ducts have a *secretory* function. The glandular tissue is known as the *parenchyma*, the connective tissue as the *interstitial tissue* of the gland

The smaller intralobular (salivary) ducts are lined with columnar epithelium whose cells contain two zones, one on either side of the centrally situated nucleus.

38 Flint, 1902

The distal zone or free extremity of the cell is finely granular, the proximal zone or base presents a characteristic striated appearance which is apparently due to a fibrillar structure of the cytoplasm in this portion of the cell. The basal fibrillae are probably, in part at least, the mitochondria which are present in all functionally active cells. The epithelium is easily detached from its basement membrane by the artificial contraction of the tissues during fixation and hardening.

The lumen of the ducts is of considerable diameter and contains the reticulated or granular particles of the secretion. The larger ducts lie in the connective tissue septa which invest the lobular groups of acini. Each of these groups is derived from the ramifications of the terminal branch of an interlobular duct which enters the lobule to divide into numerous intralobular ducts, and secondarily, through a short intermediate or intercalary portion, into the secreting alveoli or acini. The intercalary ducts are lined with low cuboidal epithelium and are the smallest tubules of the gland. As the duct passes into the acinus the tubule is increased in size, and its secretory epithelium becomes taller. The tubular acinus is more or less tortuous and possesses a sacculated or alveolar appearance.

Fig. 363—Intercalary Ducts and Acini of the Human Submaxillary Gland, Corrosion Model.

F, small intralobular duct; G, intercalary duct, H, acini. Highly magnified. (Flint.)

The epithelium differs accordingly as it secretes a mucous or a serous fluid. Thus the acini are either mucous or serous secreting.

Serous Acini.—The serous acini contain pyramidal epithelial cells of sufficient height to fill the tubule almost completely; hence the lumen is very narrow. The form of the secreting cells is somewhat irregular—a fact which apparently depends upon their crowded condition within the acinus. The nucleus is situated in the central portion or in the proximal end of the cell, and is spheroidal in shape. The cytoplasm is finely granular, the granules being more prominent in the distal portion of the cell.

The epithelium rests upon a basement membrane within which, beneath the bases of the secreting epithelial cells, are certain flattened *basket-cells* which here and there send short processes between the cells of the secretory epithelium and thus provide cup-like depressions which receive the bases of the secreting cells (Fig 371). The function and origin of these basket-cells is not at present known. They are readily recognized by their deeply stained and flattened nuclei which are contained within the thin cytoplasmic cell body. They may be immature acinal cells, destined to replace worn-out secretory cells. More probably they represent myo-epithelial elements, homologous with the similar cells of the secretory portions of the sweat glands, the mammary glands and the ceruminous glands. As such their contractile capacity would aid in the extrusion and propulsion of the secretion.

The appearance of the secreting epithelium varies with its activity. During rest the granular secretion accumulates within the cell, until the nongranular zone is reduced to a narrow rim at its basal extremity and the nucleus is obscured and

pushed somewhat basalward. The cell becomes therefore much swollen and the alveolar lumen almost obliterated. During activity the *zymogen* granules are discharged into the lumen; the cell shrinks and becomes clearer; the nucleus appears more distinct, and the granular zone becomes progressively narrower, the basal nongranular zone being correspondingly increased in breadth. In this basal zone elongated granules have been demonstrated, which in part are to be regarded as prozymogen (basal filaments of Solger), in part as mitochondria.
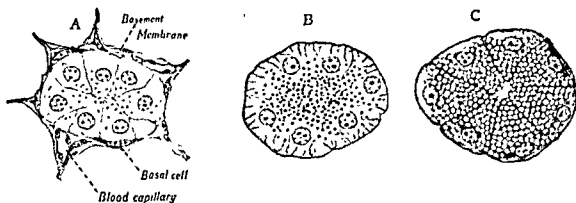
FIG. 364—SEROUS ACINI FROM PAROTID GLAND OF MAN, SHOWING THREE SUCCESSIVE STAGES OF SECRETORY ACTIVITY.

In acinus B the zymogen granules and the basal prozymogen filaments are conspicuous. In acinus C the granules have liquefied and the secretion droplets are passing into the lumen. (Hardesty.)

The serous cells are provided with systems of secretory canaliculi which, beginning at the glandular lumen, invest the cell with a network of canals which lie in the intercellular substance and may even send short offshoots or intracellular canaliculi into the body of the cell itself. These canaliculi are considered to be characteristic of the serous acini and are not found in relation with the cells of the mucous acini (Fig. 366).

Mucous Acini.—The mucous acini may contain only mucous-secreting epithelium, or they may also include certain finely granular acidophil cells which resemble the epithelium of the serous glands. The former variety of acinus is found in the mucous glands at the base of the tongue and in the soft palate; the latter in the sublingual gland, in the lingual glands of Nuhn, and in the mucous glands of the lips and cheeks.

The serous appearing cells of the latter form of mucous acinus are frequently arranged, as crescentic groups bordering upon the adjacent mucous cells. Such groups are known as the *demilunes* (of Heidenhain) or *crescents* (of Gianuzzi, Fig. 365). They occur at the periphery of the acinus, their base being applied to the membrana propria, their inner margin sometimes reaching the glandular lumen, but more frequently separated therefrom by the overlapping of the adjacent mucous cells The demilunes are frequently found at the blind extremity of the secreting acinus, but they may also occur along its sides.

The nature of the demilunes is the subject of considerable discussion. Heiden-

hain [37] first advanced the theory that the mucous cells were destroyed during secretion, and that the function of the demilunes was therefore to replace the disintegrated mucinous cells This theory has been practically abandoned, for no one has yet demonstrated active cell division in the demilunes, a process which would necessarily be concomitant with the rapid development of mucous cells from demilune cells.

Hebold (1879) is responsible for the theory, strongly supported by Stohr, that the demilunes represent an inactive, the mucous cells an active phase of mucous secretion. The easy demonstration of intermediate stages in many mucus-

FIG. 365 —FROM THE SUBLINGUAL GLAND OF MAN

a, salivary intralobular duct; *c*, acinus whose cells contain no mucus; *s*, mucous acini, at *s'* with a demilune; *sz*, mucous cells in the duct. ×500. (Kolliker.)

secreting glands lends strong support to this theory, and in the present state of our knowledge it seems beyond doubt that such a process actually occurs in at least some of the mucus-secreting glands

A third theory, advanced by Solger [38] and stoutly supported by Krause [39] and others, considers the demilunes to be true secreting cells which form a serous secretion and are therefore functionally independent of the mucinous cells. This theory receives strong confirmation in the fact first observed by Cajal (1889) and since that time repeatedly demonstrated, that the demilunes, like the true serous cells, are provided with a system of intercellular secretory canaliculi by which they are placed in relation with the glandular lumen. Moreover, Krause was able to demonstrate that granules of sodium indigo sulphate were secreted by these cells, as also by the true serous cells and the striated epithelium of the intralobular ducts. Finally, electrical stimulation of the chorda tympani nerve in the cat causes changes

[37] Heidenhain, 1869
[38] Solger, 1894
[39] Krause, 1895, 1901.

in the alveolar cells of the submaxillary gland, while similar stimulation of the cervical sympathetic trunk causes the appearance of cytoplasmic vacuolations in the demilune cells.[40]

The mucus-secreting cells examined in the fresh state present a clear, highly refractive appearance. They closely resemble the typical goblet cells, but instead of being isolated among the granular serous cells, they may invest the entire acinus, or even the whole of a small lobule may contain only mucus-secreting cells.

After the customary preparation by fixation and staining, the mucous cells present a coarse basophilic reticulum which occupies the distal portion of the cell. Coarse granules, with proper fixation and in fresh tissue as well, can be demonstrated within the meshes of the reticulum. These granules are readily colored by the so-called specific mucous stains (Mayer's muchematein and mucicarmine, safranine, and thionin).

In the mucous cells the nucleus is crowded to the base or proximal end of the cell and flattened against the basement membrane. It is surrounded by a small remnant of finely granular cytoplasm, which, after the discharge of the mucus during secretion, is presumably capable of reloading the cell with its *mucinous content*.

Fig. 366.—Mucous Acini of the Retrolingual Gland of the Rat.

The ducts and secretory capillaries have been blackened. *r*, demilunes with secretory capillaries; *s*, mucous cells. Golgi method. ×500 (Kölliker.)

We will now consider the more important peculiarities of each of the larger salivary glands.

Parotid Gland.—This is the largest of the salivary glands and in man, sheep,
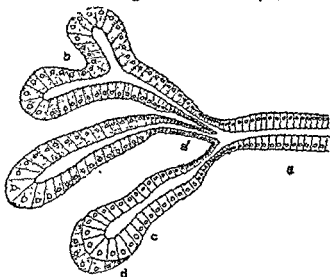
Fig. 367.—The Arrangement of the Cells in a Mixed Salivary Gland.

a, intralobular duct; *a'*, intercalary duct; *b*, serous-secreting tubules; *c*, mucus-secreting tubules; *d*, demilune. (Krause)

[40] Rawlinson, 1933
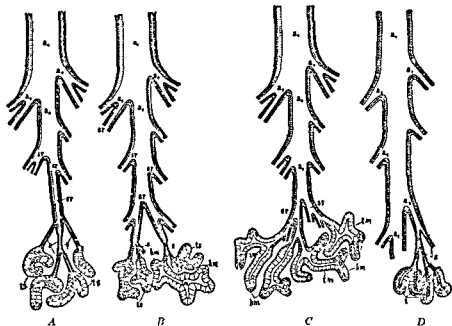
FIG. 368.—DIAGRAMS OF *A*, PAROTID GLAND; *B*, SUBMAXILLARY GLAND; *C*, SUBLINGUAL GLAND; AND *D*, PANCREAS. (Sobotta.)

a_1, interlobar duct; a_2, interlobular duct; *sr*, salivary intralobular duct; *s*, intercalary duct; *hm*, demilune; *ts*, serous alveolus; *tm*, mucous alveolus.

dog, cat and rabbit is purely a serous-secreting organ However, in sheep, dog and cat it contains also a variable number of mucous alveoli during the first year; these degenerate and entirely disappear during the second year.[41]

It is situated in front of the external ear, and overlaps inferiorly both faces of the upper portion of the ramus of the mandible A variable number of small accessory lobules, including mucus-producing alveoli, lie along the course of the main parotid (Stenson's) duct. The latter opens into the mouth at the level of the second upper molar. The parotid is invested by a dense
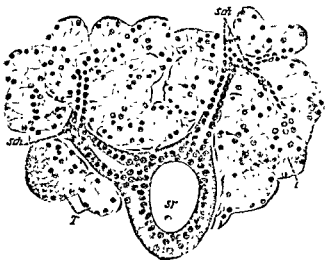
FIG 369—FROM A SECTION OF THE HUMAN PAROTID GLAND.

l, lumen of a serous acinus; *sch*, intercalary duct; *sr*, intralobular duct; *T*, secreting acini. Hematoxylin and eosin. ×280. (Sobotta.)

fibro-elastic sheath, septa from which divide the gland into lobes and lobules. The lobes and lobules are firmly united by the dense but narrow bands of connective tissue; these contain the larger ducts, blood vessels, lymphatics, and a few small ganglia.

The secreting acini are relatively long and tortuous; they are frequently branched or forked. Because of the relatively low height of their serous-secreting cells the acini appear slender and their lumen is irregular, indistinct, and very nar-

[41] Brock and Trautmann, 1914

row. The "basket cells" upon which the secreting cells rest are highly developed in the parotid and often form a complete investment for the acinus.

The acini of the parotid are all of one type. The only other tubules within the lobules of this gland are the intercalary and the intralobular or *salivary* ducts. The former are characterized by their very narrow caliber and low epithelium. They are slender tubules which open on the one side *from* the acini and on the other *into* the branched terminals of the more spacious salivary ducts. The salivary (secretory) portion of the intralobular duct has a somewhat greater diameter also than the excretory portion, which is histologically similar to the interlobular ducts. In the parotid the salivary ducts are relatively short as compared with the intermediate ducts, but are readily recognized by their striated columnar epithelium, which is deeply colored by acid dyes (eosin, etc.), and are thus sharply distinguished from the secreting cells of the acini, which stain poorly with these dyes

Submaxillary Gland.—In man and in most mammals this organ is a mixed salivary gland; that of the bear and dog contains the largest, that of man and the apes the smallest proportion of mucous acini.[42] In man the proportion of mucous to serous alveoli is about one to five. In the rabbit, rat and guinea-pig the submaxillary is a serous-secreting gland, containing only serous acini. The submaxillary gland is situated in the floor of the mouth under the posterior portion of the mandible. The main submaxillary (Wharton's) duct opens into the mouth one on either side of the frenulum of the tongue, sometimes joined by the duct of the sublingual gland.

The serous acini of .the submaxillary are shorter and less typically tubular than those of the parotid, and they are lined with taller secreting cells. The diameter of the acinus is therefore slightly greater in this gland than in the parotid. Its mucous acini contain a relatively large proportion of demilunes.

The intercalary ducts are considerably shorter than in the parotid, while the salivary intralobular ducts are much longer in the submaxillary. The interlobular connective tissue is not quite so delicate as in the parotid. It contains many sympathetic ganglia of relatively large size. Small lamellar corpuscles of simple construction are occasionally found in the interlobular connective tissue (Krause).

Sublingual Gland.—This is the smallest of the three pairs of large salivary glands. It is not invested by a distinct capsule. It lies under the floor of the mouth anteriorly, one on either side of the frenulum. It is a mixed gland in man, dog, cat, sheep, pig and rabbit It differs from the submaxillary, however, in that all of its acini are mucous. It becomes "mixed" by reason of the presence of very many demilunes (serous cells). Although isolated sections which pass through the larger collections of demilune cells may appear as sections of serous-secreting tubules, if examined in longitudinal section or by reconstruction the true mucous character of each lobule is apparent Many of the terminal acini of the sublingual gland, however, although much branched, contain no demilunes. In the guinea-pig demilunes do not occur in association with the mucous acini. The basket cells are readily recognized in the acini of this gland though they are less highly developed

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[42] Krause, 1897.

FIG. 370—SECTION OF HUMAN SUBMAXILLARY GLAND, SHOWING INTRALOBULAR DUCT, PRE-
DOMINATING SEROUS ACINI AND A SMALL GROUP OF MUCOUS ACINI ×800.

here than in the parotid. Its intralobular duct system lacks intermediate ducts, and
is largely of the salivary type.

Accompanying the sublingual gland proper, or larger component, are a variable
number (5 to 20) of accessory sublingual
glands of various sizes. They consist largely
of mucous alveoli, each gland opening into
the mouth by an independent duct. The duct
of the sublingual proper (duct of Bartholin)
opens at the side of the frenulum.

Blood Supply.—The salivary glands pos-
sess a rich blood supply. The arteries
accompany the glandular ducts within the
interlobar and interlobular connective tissue,
and thus reach all the lobules of the gland.
Small arterial twigs enter the lobule from all
sides and form a rich capillary plexus in the
delicate connective tissue coats of the acini.
The capillaries are thus brought into intimate

FIG. 371—TANGENTIAL SECTION OF SER-
OUS ALVEOLUS OF SUBMAXILLARY GLAND
OF MAN SHOWING TWO BASKET (MYO-
EPITHELIAL) CELLS.

Iron hematoxylin stain (Zimmermann)

relation with the secreting cells, from which they are only separated by the base-
ment membrane of the acinus. The veins return by a similar course, the smallest

venules passing out of the lobule into the connective tissue septa in which they retrace the course of the arteries.

Lymphatics.—Lymphatics are relatively few and are for the most part confined to the interlobular septa. Here they form cleft-like spaces which lead to true lymphatic vessels and so on to the lymph nodes of the cervical region.

Nerve Supply.—The salivary glands are abundantly supplied with nerves, which are derived from both sympathetic and cerebral trunks. They are distributed to the walls of the blood vessels and ducts, and to the secreting cells of the acini. The nerve trunks are found in the interlobular connective tissue where they are supplied with small ganglia which are most abundant in the submaxillary and least numerous in the parotid gland.

The sympathetic fibers which innervate the blood vessels proceed from the superior cervical ganglion. They are believed to be vasodilator fibers. The cerebral nerves, which supply fibers to the gland cells, are the facial and the glossopharyngeal.

FIG. 372.—RECONSTRUCTION MODEL OF THE SUBLINGUAL GLAND OF MAN

An intralobular duct terminating in salivary ducts and acini. ×285. (Maziarski.)

The parotid gland is supplied by the glossopharyngeal; the fibers (secretory and vasoconstrictor) passing by way of the tympanic nerve (nerve of Jacobson), small superficial petrosal, otic (sympathetic) ganglion, and the auriculotemporal branch of the inferior maxillary division of the trigeminal nerve. The submaxillary and sublingual glands receive their secretory fibers and vasoconstrictor fibers from the trigeminal nerve, by way of the chorda tympani nerve and the submaxillary (sympathetic) ganglion. The fibers beyond the otic and submaxillary ganglia are believed to be true postganglionic fibers; that is, axons of cell bodies situated in these ganglia. Sensory fibers are said to pass to the ducts.

FIG. 373.—NERVE ENDINGS IN A SALIVARY GLAND.

H, demilune; I, secreting acini; n, nerve fibrils. Highly magnified. (Retzius, from Rauber.)

Delicate fiber bundles from the interlobular nerve trunks enter the lobules and form a plexus of naked fibrils about the walls of the acini, known as the *epilemmal plexus*, from which terminal fibrils pierce the basement membrane and as *hypolemmal fibers* end in contact with and between the secreting cells. Small terminal expansions, varicosities, or end-knobs are found in the course of the hypolemmal fibers.

THE PANCREAS

The pancreas is a flat elongate body lying behind the stomach between the loop of the duodenum and the spleen. It arises from two primordia: a smaller from the common bile duct (ventral pancreas), and a larger from the duodenum (dorsal pancreas). These primordia are located in the ventral and dorsal mesentery, respectively. They subsequently fuse to form a single organ drained mainly by the duct of the ventral component, which has meanwhile made an anastomosis with that of the dorsal component, the latter proximal to the anastomosis nevertheless commonly remaining pervious and functional The pancreas bears a close structural resemblance to the salivary glands, more especially the parotid. It is
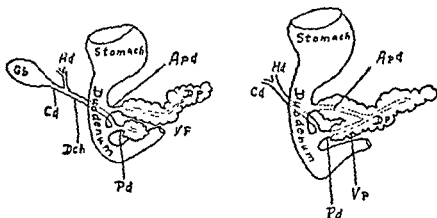
FIG 374—EARLY STAGES IN THE DEVELOPMENT OF THE PANCREAS, ILLUSTRATING CONDITIONS IN THE FIVE AND SEVEN WEEKS' OLD HUMAN EMBRYOS.

Dp, dorsal pancreas , *Vp*, ventral pancreas , *Pd*, pancreatic (Wirsung's) duct ; *Apd*, accessory pancreatic (Santorini's) duct , *Dch*, ductus choledochus , *cd*, cystic duct ; *Hd*, hepatic duct (Adapted from Kollman)

enveloped by a thin areolar capsule, extensions from which divide the organ into lobes and lobules. It is a compound tubulo-acinose gland which contains an immense number of small lobules associated into lobes and which pours its secretion into the lumen of the duodenum by means of the chief (Wirsung's) and accessory (Santorini's) pancreatic ducts. The lobules are united by a delicate and relatively very loose fibro-elastic connective tissue. The capsule lacks a peritoneal investment except on the anterosuperior and the inferior surfaces.

The ducts of the pancreas branch and arborize in the same manner as those of the salivary glands. The interlobular ducts are lined with a single layer of columnar cells; in the larger divisions (interlobar ducts) occasional goblet cells are found. The wall of the interlobular pancreatic ducts is much thicker than in those of the salivary glands, for they possess a much thicker connective tissue coat, in which are also many longitudinal smooth muscle fibers

On entering the lobule the duct is immediately transformed into the intercalary (intermediate; junctional) type. In the pancreas there are no specialized intralobular ducts lined with columnar striated epithelium as in the salivary glands.

The intercalary ducts are very slender tubules which are lined with low columnar or flattened epithelium. Because of the absence of larger intralobular ducts the intercalary portions are relatively very long and much branched.

On approaching its termination the lining cells of an intercalary duct are still more flattened and often acquire a considerable breadth. They are elongated in the direction of the long axis of the tubule, and in surface view have an irregularly polygonal outline (Bensley). They pass into the acini in a peculiar manner. Instead of offering a direct transition from the duct epithelium to that of the acinus the cells of the former frequently appear as if telescoped into the lumen of the acinus. Thus the *centro-acinose cells* (of Langerhans) are produced, and consequently the centro-acinose cells correspond closely in appearance with those of the intercalated ducts. They seem to occupy the lumen of the acinus, and are only separated from the distal ends of the acinose cells by the secretory capillaries which place the secreting cells in communication with the lumen of the duct. The centro-acinose cells are characteristic of the pancreatic acini.
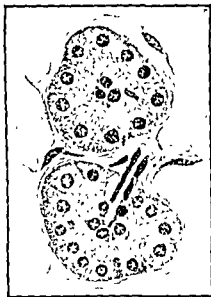
Fig. 375.—Two Acini from Human Pancreas, Showing the Relation of the Intercalary Duct to the Centro-acinose Cell Groups. (Hardesty.)

Fig. 376.— Reconstruction Model of the Human Pancreas

The interlobular duct gives off long intercalary ducts, which, after branching, end in the acini. ×344. (Maziarski)

The Acini.—The acini of the pancreas possess an irregular tubular form with frequent alveolar dilatations. Their lining epithelium rests upon a reticular basement membrane within which are thin myo-epithelial basket cells. A delicate connective tissue stroma invests the acini.

The secreting cells are tall and irregularly columnar or pyramidal in shape. Their nucleus lies in the proximal third of the cell and is surrounded by reticular or very finely granular cytoplasm. The cytoplasm of the inner zone of the cell, on the other hand, is filled with coarse zymogen granules whose number is dependent upon the activity of the gland. During fasting the granules accumulate until eventually they almost completely fill the cell, but during digestion they disappear with the discharge of the secretion, the width of the granular zone gradually decreasing, that of the nongranular fibrillar basal zone being correspondingly enlarged (Figs. 378, *A* and *B*).

With the increased breadth of the basal zone during secretion, there appears in this portion of the cell a structure which has been described by Nussbaum [43] as the *Nebenkern*, and which has been carefully studied by Mathews.[44] This is a spheroidal basophil body which lies near the nucleus and is frequently surrounded by a clear area of cytoplasm (Fig. 379). Its origin and function are undetermined and it is possible that several distinct bodies have been included under the name.
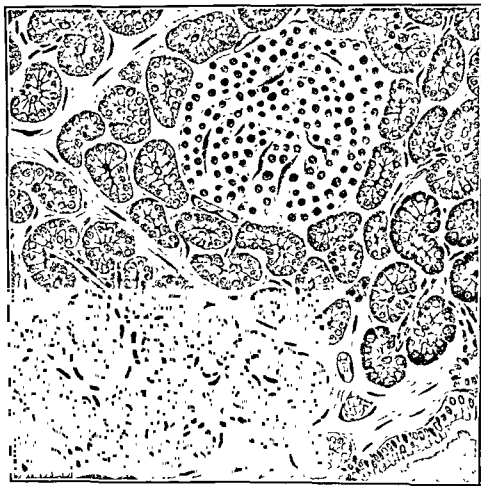
FIG. 377—SECTION OF HUMAN PANCREAS, SHOWING ONE ISLET (OF LANGERHANS) AND NUMEROUS ACINI, SEVERAL WITH ASSOCIATED INTERCALARY DUCT.

Portion of an interlobular duct appears at the lower right hand border. (Hardesty)

Ogata [45] considers that it is derived from the nucleus by the extrusion of its plasmosome, an opinion which seems to be shared by von Ebner.[46] The studies of Mathews have shown that at least in certain instances it is distinctly fibrillar and suggest that it may be concerned with the mechanism of secretion. It most probably represents a postsecretion remnant of ergastoplasmic basal filaments.

In addition to this fibrillar complex of basophilous substance, there may be seen

[43] Nussbaum, 1885
[44] Mathews, 1899.
[45] Ogata, 1883.
[46] von Ebner, 1902.

in appropriately fixed and stained preparations, another group of fibrils, the mito-chondria. These can be seen in fresh acinose cells and in tissue preserved in neutral fluids, when they also give to the basal portion of these cells a striated appearance. These basal bodies have been extensively studied by Bensley[47] in the pancreas of the guinea-pig, and their independence from the basal filaments of Solger estab-lished. Mislawsky[48] also studied the mitochondria in the acinose cells of the rabbit's pancreas. He finds no evidence to indicate that they segment into the zymogenic granules. They are described as interstitial elements of the protoplasmic reticulum, more probably connected with the general cell metabolism. There is apparently no good evidence in support of the idea that either the basal filaments of Solger or the mitochondria give origin to secretory granules, by a process of segmentation.
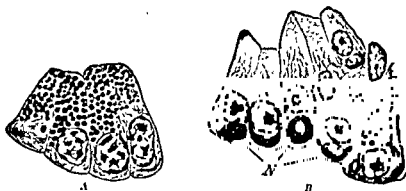
FIG 378 — CELLS FROM PANCREAS OF NECTURUS.

A, after rest, and filled with zymogen granules; *B*, after activity, showing the presecretion (basal, ergastoplasmic) filaments, and the so-called nebenkern (*N*). (Mathews.)

Pancreatic Islets.—The lobules of the pancreas contain, in addition to the acini and ducts, certain larger and smaller spheroidal collections of polyhedral cells which lie in the inter-acinose connective tissue, the *pancreatic islets* (*islands of Langerhans; intralobular* or *interalveolar cell groups*). The islet cells are arranged in irregular cords, frequently only two cells deep, lying in the meshes of capilliform sinusoids, from which they appear to be separated by little more than the endothelial wall. The cells are divisible into two distinct, apparently inde-pendent types, on the basis of their granular content.[49] The *A* and *B* granules differ morphologically and microchemically; it is suggested that they indicate twofold secretion. Cells with *B* granules are the smaller and more numerous cells of the islets. Granules of the *A* type are preserved by alcohol, those of the *B* type by chromesublimate solutions; both varieties are dissolved by acetic acid The granules of the islet cells of both types differ markedly also from those of the acinose cells. The islet cells of B type are believed to be the active elements in the elaboration

[47] Bensley, R. R., 1911
[48] Mislawsky, 1913
[49] Lane, 1907

of insulin. Bensley [50] discriminates a nongranular type of cell. This "C" type of cell may signify the indifferent precursor of cells A and B. Bloom [51] has described a third type of granular islet cell ("D") of unknown significance but probably not identical with the C type of Bensley.
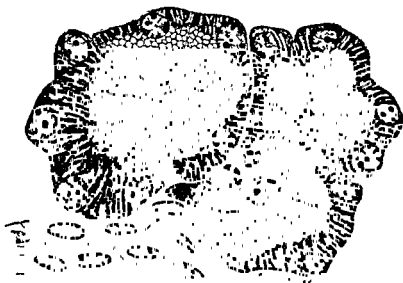
FIG. 379—TWO ADJACENT ACINI FROM THE GUINEA-PIG'S PANCREAS.

The one at the right shows an entering intercalary duct and two centro-acinose cells. The acinose cells are filled proximally with a basophilous substance (basal filaments), and contain distally numerous alveoli, the representatives of dissolved zymogen granules. ×1200 (Bensley.)

The islets are of various sizes, ranging from those with only a few or even a single cell to those with many cells (3 millimeters in diameter). The number of islets also varies greatly in different individuals. Thus De Witt [52] estimated the
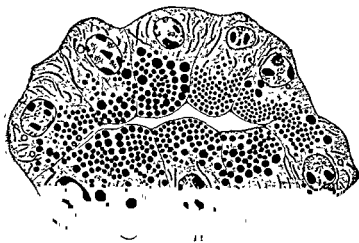
FIG. 380—SECTION OF AN ACINUS FROM THE GUINEA-PIG'S PANCREAS, SHOWING THE BASAL MITOCHONDRIAL CONTENT AND THE CENTRAL ZYMOGEN GRANULES.

Bensley's mitochondrial technic ×1200 (Bensley.)

[50] Bensley, R. R., 1915.
[51] Bloom, 1931
[52] De Witt, 1906

amount of islet tissue in three apparently normal subjects at 1–25, 1–50 and 1–125 of the total volume of the pancreas. By means of intravitam stains (neutral red and janus green), Bensley succeeded in staining differentially the islets of the guinea-pig's pancreas. He counted from 13,000 to 56,000 in different specimens. Clark [53] employed this method in a study of human pancreases secured shortly after death, and estimates the average number of islets at 12 per milligram. In one male subject of twenty-four years and 140 pounds weight, he estimated the total number of islets at 1,760,000; in another of twenty-nine years and 135 pounds weight, only 662,166. Opie [54] first observed that the islets were more abundant in the tail and least abundant in the head of the pancreas; this observation is confirmed by both Clark and Bensley. Laguesse [55] described the islets in continuity with the ducts of the acini. Such continuity is described also by Bensley for many of the islets in the guinea-pig's pancreas. Bensley's studies have disclosed these further points of

FIG. 381.—INTERCALARY DUCT WITH BRANCHES, FROM PANCREAS OF GUINEA-PIG, SHOWING HIGHLY BRANCHED TUBULES CONNECTED WITH THE DUCT AND WITH AN ISLET.

Intravitam staining with pyronine and neutral red. ×50. (Bensley.)

relationship between the islets and the zymogenous parenchyma: Islets may be located (1) in the interlobular connective tissue, but connected with the duct system by solid cords; (2) in the lobules, unconnected with the acini (encapsulated), but directly connected with the interlobular duct system; (3) in the lobules, and in connection with either acini or ducts or both (these include the great majority); and (4) islets unconnected with either ducts or acini, both in the interlobular connective tissue and in the acinose parenchyma.

The tubules (intercalary ducts) are said to branch and anastomose freely and to be capable of differentiating either into acini, or islets, or both. They may produce also small mucous glands which open into the tubules; and single islet cells may be formed along the ducts. Notwithstanding their intimate developmental

53 Clark, 1913

54 Opie, 1900.

55 Laguesse, 1911.

relationship the islets remain isolated from the general exocrine parenchyma, since the lumen of the connecting tubules does not penetrate its substance. There is no satisfactory evidence to show that islet tissue may be increased or diminished, or that acinose tissue may change into islet tissue, or *vice versa*, concomitant with experimentally induced alterations in nutritive and functional conditions, as has been repeatedly claimed; nor is there evidence of a transition between islet and acinose cells. Islets and acini have a common embryonic origin, but once differentiated they are not capable of transformation one into the other.[56] The islets appear in the human pancreas when the embryo attains a length of 50 millimeters.

Both acinose and islet tissue may regenerate extensively. Experimental reduction of pancreatic tissue in the rabbit by means of excisions or duct ligation stimu-
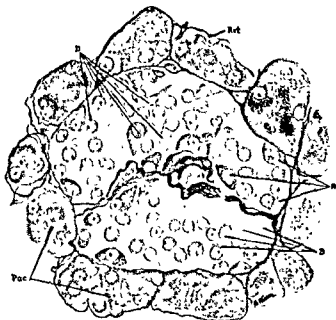
FIG 382—ISLET OF LANGERHANS OF HUMAN PANCREAS, SURROUNDED BY ACINI (PAC).

The pancreatic islet comprises three types of granular cells, *A*, *B* and *D*. The reticular fibers are stained blue. Mallory-azan stain. (Bloom)

lates hitherto indifferent duct epithelium to differentiate into islet and acinose cells. Grauer [57] reports a case in which he reduced the pancreas of a rabbit to only a system of branching ducts, and secured restoration to approximately normal conditions within twenty-five days.

The islets constitute an endocrine organ secreting *insulin*, a substance essential for the normal metabolism of sugar. Opie and many others have shown that when the pancreas is removed, a form of diabetes follows, characterized by the appearance of sugar in the urine. When the pancreatic duct is simply ligated, the flow of pancreatic juice is checked and atrophy of the acinose tissue ensues, but no disturb-

[56] Bensley, R R, 1911.
[57] Grauer, 1926.

ance in carbohydrate metabolism results, nor is any alteration produced in the islet tissue. Moreover, in cases of death following diabetes mellitus, Opie demonstrated gross degenerative changes. Homan's [58] experiments have extended the evidence in support of the conclusion that the islets are concerned in the metabolism of sugar. When more than three-fourths of the pancreas was removed in cats, the main duct being left intact, fatal diabetes occasionally followed. Microscopic examination of the islets revealed the following conditions: (1) in those instances where diabetes did not follow the operation, the islet cells showed signs of overactivity indicated in part by a disappearance of secretory granules; (2) in the subjects which died from diabetes following the operation, the islet cells showed degenerative changes, the acinose tissue having remained unaltered.

Blood Supply.—The large blood vessels of the pancreas accompany the interlobular ducts, but after repeated subdivision these vessels part company, and the smaller arteries pursue a separate course through the interlobular connective tissue. Thus they reach all portions of the gland and supply capillaries to the intralobular connective tissue about the acini. Certain arterial branches also enter the islets and form an especially rich plexus of broad capillaries (sinusoids) within these cell groups. The veins return the islet blood by a similar course.

Lymphatics.—The lymphatics are mostly confined to the interlobular tissue, where they are in relation with the blood vessels.

Nerves.—The nerves are derived from the sympathetic system, and occur as small trunks within the interlobular connective tissue. Numerous small ganglia occur in their course. As in the salivary glands the nerves supply the vascular walls. About the secreting acini they form a delicate network of naked fibrils, from which end branches penetrate the basement membrane and terminate upon the secreting cells. Lamellar corpuscles are occasionally found in the interlobular connective tissue of the pancreas.

Résumé.—Finally the attention of the student should be specially directed to the presence of the pancreatic islets, the centro-acinose cells, the very distinct inner granular and outer fibrillar zones of the secreting cells, the thick walls of the interlobular ducts, the absence of intralobular ducts except of the intercalary type, and the loose character of the interlobular tissue as the distinguishing characteristics of the pancreas.

THE LIVER

The liver is the largest gland of the body, and may be classed as a peculiar form of compound tubular gland whose cells resemble the serous-secreting type. The organ is invested with a connective tissue sheath, the greater portion of which is clothed with peritoneal epithelium. From this connective tissue capsule, fibrous bands or septa are continued into the substance of the organ and permeate to all its portions. These processes of connective tissue, collectively forming the *capsule of Glisson*, are most abundant at the transverse fissure where they contain the large blood vessels and hepatic ducts—this fissure serving as a hilus for the organ. The

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[58] Homan, 1914

liver is very irregular in outline and shape, and comprises four lobes of unequal size. In the adult its weight is about one-fortieth that of the body, about 3 to 3¾ pounds. The parenchyma of the organ arises from a tubular outgrowth of the embryonic duodenum, hence entodermal. The interstitial tissue develops in part from the mesenchyma of the caudal layer of the primitive diaphragm (septum transversum) and of the intervening ventral mesentery throughout which the
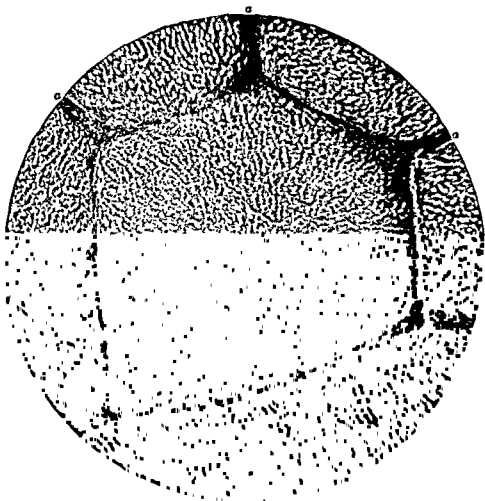
FIG 383—A LOBULE OF THE PIG'S LIVER; THE CENTRAL VEIN LIES IN THE MIDDLE OF THE FIGURE.

a, capsule of Glisson. Hematein and eosin. Photo ×115.

entodermal tubules ramify, and in part (the reticulum) from endothelium of the original venous sinusoids.

The liver is dependent for its structural characteristics upon the peculiar disposition of the connective tissue of Glisson's capsule, as also of the blood vessels whose branches it contains By these tissues the substance of the liver is extensively subdivided into minute collections of hepatic cells, each group forming an anatomic unit, the *hepatic lobule,* which in addition to the hepatic cells contains a connective tissue reticulum and the smaller blood vessels and secretory capillaries (bile canaliculi).

The hepatic lobules are of cylindrical shape, about 2 millimeters in length and 1 millimeter in diameter (Bailey). In transverse section they present a polygonal (hexagonal or pentagonal) outline. In the dog they are short polyhedra about 0.7 millimeter high, and 0.7 millimeter in diameter; the entire liver containing 480,000.[59] They are analogous to the lobules of compound tubulo-acinose glands, inasmuch as they contain the secreting parenchyma of the organ. They are very different
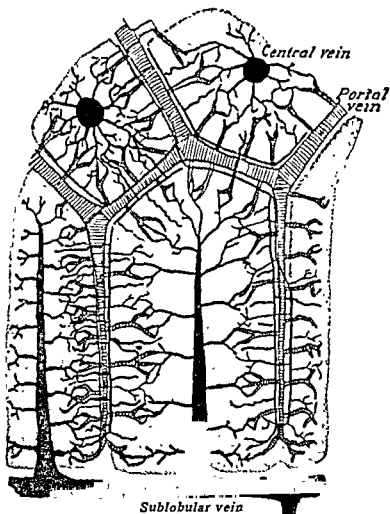
FIG. 384.—LIVER LOBULES, THE UPPER TWO CUT TRANSVERSELY, THE LOWER LONGITUDINALLY.

The portal veins are blue striped; the hepatic veins (central with branches, and sublobular) are solid blue; the hepatic arteries are red; and the bile canals black. (Merkel.) Cells not indicated

in the arrangement of the secreting cells which, in the human liver, do not present either a tubular or acinose structure, but form solid cell columns. Thus in the human liver the tubular character of the gland is scarcely apparent, yet in the liver of many of the lower animals, notably in that of the turtle and frog, the cells form typical tubules within the indistinct hepatic lobules.

59 Mall, 1906

The bile formed by the liver cells is conveyed to the duodenum by an excretory system, beginning with innumerable interlobular bile ducts which receive the intralobular secretory capillaries and, leaving the lobule from all its sides, find their way through the interlobular connective tissue of the capsule of Glisson and unite with their fellows to form larger and larger bile ducts. These finally join to form the main excretory or *hepatic duct*. The latter unites with the cystic duct of the gallbladder to form the common *bile duct through which the bile reaches the intestine.* The gallbladder—which is in principle a diverticulum from the hepatic duct—is simply a reservoir for the storage of bile; it is absent in some animals, for example, the horse and the elephant. In all their course the bile ducts are in close relation with the radicles of the portal vein and of the hepatic artery—the *group of vessels which, together with their supporting (interlobular) connective tissue and the included nerve and lymph channels, form the so-called portal canals.*

Hepatic Connective Tissue.—The hepatic connective tissue, or the supporting tissue of the liver, includes the capsule of the organ and the capsule of Glisson—*the latter forming a framework throughout the liver and inclosing its hexagonal lobules*—together with the more delicate intralobular reticulum. These tissues convey the blood vessels, lymphatics, nerves, and bile ducts.

FIG 385.—FROM A SECTION OF THE TURTLE'S LIVER, SHOWING THE TUBULAR ARRANGEMENT OF THE PARENCHYMA.

a, blood capillary, partially filled with clotted blood; *b*, vascular *endothelium*; *c*, granular central portions of the hepatic cells; *d*, peripheral portion of the hepatic cells Osmium tetroxide; carmine. ×400. (Shore and Jones)

The fibrous framework, which forms both the outer fibrous capsule of the liver and the capsule of Glisson, contains both collagenous and elastic tissue. Elastic fibers are fairly abundant—a fact which sharply contrasts with the complete absence of these fibers from the interior of the hepatic lobules.

The intralobular connective tissue is extremely delicate, and consists of very fine reticulum fibrils and *stellate cells* which form a delicate stroma, in which the capillary blood vessels and columns of liver cells are suspended. The anastomosing strands of reticulum converge from the periphery toward the center of the lobule, thus following the course of the blood capillaries and cell columns. This reticular tissue exists in so small a quantity and is so extremely delicate that it can scarcely be discovered in the minute clefts between the cell columns and the blood capillaries. However, it can be readily studied after removal of the liver cells, as by artificial digestion. It differentiates, at least in part, from the endothelium of the original venous sinusoids. The stellate cells seen in Golgi preparations also represent endothelial elements. The endothelial cells of the intralobular capillaries are known as the *cells of von Kupffer* and are actively phagocytic.

The volume of the interlobular connective tissue which forms Glisson's capsule varies greatly in different animals. In the liver of the pig and the camel this

tissue is very extensive, and forms a complete investment for each lobule. In man it is very limited in amount and is confined to minute areas between the adjacent angles of the lobules, with an occasional fragment separating the lateral surfaces of neighboring lobules. It is in the latter portions, *viz.*, between the opposed surfaces of the lobules, that the branches of the hepatic veins (sublobular veins) are found. The interlobular veins, the subdivisions of the portal vein, together with the bile ducts and the branches of the hepatic artery are found at the angles of adjacent lobules. Hence the *portal canals*, which contain these vessels, should always be sought in this location, while the sub-lobular veins, which run alone and form no part of the portal canals, will be found between the opposed surfaces of the lobules.

FIG. 386.—THE RETICULUM OF THE DOG'S LIVER.

a, central vein; *b*, capsule of Glisson at the margin of the lobule. Gold chloride. ×120. (Böhm and von Davidoff.)

The capsule of Glisson also contains many lymphatic vessels and unmyelinated nerve fibers.

Hepatic Lobule.—The lobule is the structural unit of the liver and consists chiefly of hepatic cells which are arranged in radiating cords. In shape the lobule is an irregularly hexagonal truncated pyramid, the exact number of its faces being extremely variable. The periphery of the lobule is outlined by the connective tissue of Glisson's capsule which either completely invests each lobule, as in the pig's liver, or forms only a very incomplete investment, as in the liver of man.

FIG. 387.—GROUP OF CELLS OF HUMAN LIVER. (Hardesty)

Blood enters the lobule from the vessels of the portal canals and finds its way, through converging capillaries, constituting a venous rete mirabile, from the periphery to the center of the lobule. Here it enters the intralobular or central vein, which occupies the axis of the lobule and conveys the blood thence to the sublobular

veins, which again lie in the interlobular connective tissue of the capsule of Glisson.

The hepatic cells occupy the meshes of the intralobular capillaries (sinusoids) and are arranged in cords which radiate from the central vein toward the periphery. The frequent anastomoses of the capillaries as they approach the central vein produce great irregularities in the arrangement and length of the cell cords Each cord, however, reaches the periphery of the lobule after a more or less tortuous course, and it is here that the secretory bile capillaries, which are found

Fig 388—A Lobule of the Pig's Liver in Longitudinal Section, Showing the Relation of the Central and Sublobular Veins and the Arrangement of the Hepatic Cells

a, sublobular vein, b, capsule of Glisson. Hematein and eosin Photo. ×68.

within the cell cords, become continuous with the minute bile ducts of the portal canals

Bile Capillaries.—The bile capillaries occur as secretory canaliculi between the opposed surfaces of the hepatic cells. They are thus found within the cell cords and stand in the same relation to the hepatic cells as though each cell cord formed a tubule whose capillary lumen, the *bile canaliculus* were surrounded by only two secreting cells, whereas in other tubular glands a larger number of cells encircle the lumen of the secreting tubule. Hence the bile canaliculi and the blood

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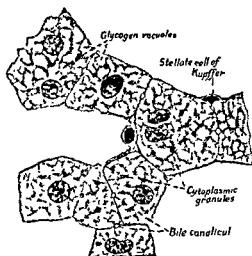
membrane may be regarded as being absent, yet there is often a sharply defined exoplasm which forms the surface of the cell and simulates a true membrane.

The nuclei of the hepatic cells are generally rich in chromatin, and stain deeply. They are situated well within the cell, but usually in an eccentric position Frequently the nuclei of the hepatic cells contain a distinct nucleolus.

The cytoplasm of the hepatic cells is finely reticular, the meshes being filled with coarse granules of irregular size. Many of these are undoubtedly *glycogenic* granules, and show a decided color reaction when treated with Lugol's solution of iodine after alcoholic fixation. The amount of glycogen present varies with the diet. After digestion and absorption of a carbohydrate meal it is greatly increased, but disappears during the fasting. Even when glycogen is quite deficient, the hepatic cells still present a granular appearance from the presence of other substances, possibly *zymogens*.
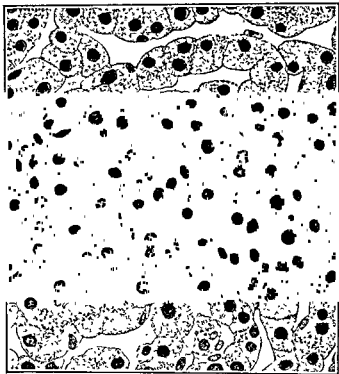
FIG. 390—SECTION OF HUMAN LIVER TISSUE, SHOWING THE CELL CORDS AND THE SINUSOIDS LINED WITH ENDOTHELIUM. ×240.

Fat Globules—Fat globules occur in hepatic cells in limited numbers, and appear to be a normal constituent. The globules vary much in size, but are all very small. Their number is also dependent upon diet and digestion. During absorption of a fatty meal, fat globules occur in considerable numbers, and are most numerous in those hepatic cells which are at the periphery of the lobule. They are not normally found in the vicinity of the central vein.

FIG 391.—FOUR ADJACENT LIVER CELLS.
(Adapted from Merkel)

Blood capillary
Bile capillary

The hepatic cells also frequently contain brown or yellowish-brown granules of ferruginous *pigment*, which are more prone to occur in the interior of the lobule near the central vein When present in considerable amount this pigment can no longer be considered a normal constituent of the hepatic cells. Mitochondria have been described in the hepatic cells [60] An intracellular canalicular apparatus can also be

[60] Policard, 1909

capillaries are never in contact, but are always separated by at least one-third to one-half the diameter of a hepatic cell. The bile canaliculus occurs on that surface of the hepatic cell which is in contact with other cells within the cord; the blood capillary, on the other hand, is in relation with that surface of the hepatic cell which forms the periphery of the cell cord.

The blood capillaries are suspended in the fine meshes of the delicate reticulum which has already been described as the intralobular connective tissue, and which

FIG 389.—A LOBULE OF THE HUMAN LIVER, SEEN IN TRANSECTION.

It is outlined by three small portal canals and contains a single central vein. Hematin and eosin. Photo. ×50

also invests the cords of hepatic cells. The reticular connective tissue is of relatively insignificant volume.

The bile capillaries are true secretory canaliculi by which the bile, after secretion by the hepatic cells, finds its way along the anastomosing cell cords to some point at the periphery of the lobule. Here the cell cord becomes continuous with a minute bile duct, the secreting cells within the lobule presenting a rapid transition to the very low columnar or flattened epithelium of the interlobular bile duct. The immediate lining of the intralobular bile canaliculus is a delicate cuticular membrane, probably the product of the hepatic cell.

Hepatic Cells.—These are large polyhedral cells which possess one, or very frequently two, spherical nuclei and a coarsely granular cytoplasm. A true cell

peculiarity consists not so much in the structure of the tissue, as in the combination of artery, duct and vein occurring in close relation, in the connective tissue at the angles of the hepatic lobules. The largest vessel in the canal is invariably the vein, the smallest the artery.

Interlobular Veins.—The interlobular veins, branches of the portal, are extremely thin-walled sinusoidal vessels. They are formed by scarcely more than the endothelial lining, which is supported by the connective tissue of Glisson's capsule. Their wall contains very little or no smooth muscle.

Interlobular Arteries.—The interlobular arteries, branches of the hepatic, are very small and are noted for their highly developed muscular coat and distinct elastic membrane. They give off minute vaginal branches which supply capillaries to the tissue of Glisson's capsule.

Interlobular Bile Ducts.—The interlobular bile ducts, tributaries of the hepatic duct, receive the bile from the intralobular bile canaliculi and convey it, through larger and larger branches, to the hepatic duct. They are more numerous than the interlobular veins and much more numerous than the interlobular arteries. Due to their frequent branching many of the portal canals as seen in transverse section contain two bile ducts. The ducts are lined with columnar epithelium whose height varies with the size of the tubule, the smallest ducts being lined with low columnar, or cuboidal, the largest with tall columnar cells. The lining epithelium of the hepatic, cystic and common bile ducts is very tall. The epithelial cells of the ducts possess characteristic spherical or ovoid nuclei which are heavily loaded with chromatin. Their cytoplasm is clear or finely reticular. The largest ducts contain a few goblet cells. Small mucous glands are found in the hepatic and common bile duct.
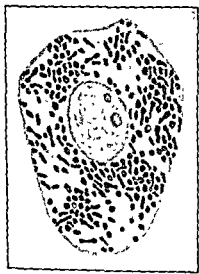
FIG 395—LIVER CELL FROM FULL TERM HUMAN FETUS, SHOWING ABUNDANT MITOCHONDRIA

Regaud's technic. (Noel and Pigedud.)
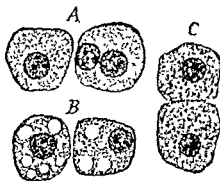
The epithelium of the interlobular bile ducts rests upon a thin basement membrane, which is surrounded by a thick fibro-elastic coat. The larger ducts are also supplied with circular smooth muscle fibers, which, in the largest branches, form a considerable coat Outside of the liver, longitudinal muscle fibers also appear in the walls of the excretory ducts, and so accumulate in the wall of the gallbladder and common bile duct as often to form a distinct layer.

demonstrated within the cytoplasm. By some these channels have been interpreted as intracellular terminals of the intercellular (intralobular) bile canaliculi, by others as fixation artifacts, and still others regard them as a trophospongium. Schäfer[61] interprets them in part as channels in relation with the blood sinusoids. Such intracellular canaliculi undoubtedly appear under certain functional conditions, but it is
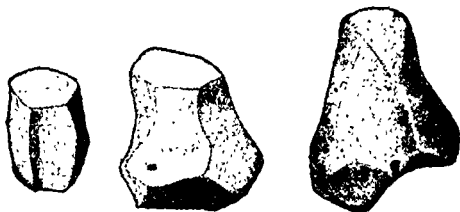
FIG. 392—ISOLATED LOBULES OF THE PIG'S LIVER. × 12.5. (Johnson.)
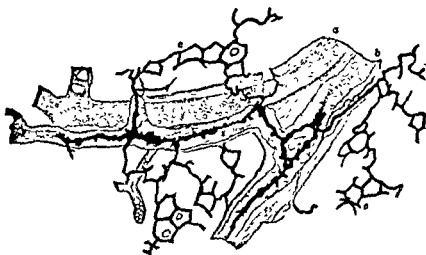
FIG 393—THE CONNECTION BETWEEN THE INTRALOBULAR AND INTERLOBULAR BILE DUCTS IN THE CAT'S LIVER.

a, interlobular vein; *b*, interlobular bile duct; *c*, intralobular bile capillaries. Golgi stain and hematein Highly magnified. (Geberg.)

uncertain whether they are definite preformed channels, or simply transitory secretory canals. Moreover, it seems probable that the canals described include structures of different significance.

Portal Canals.—The portal canals are formed by the ramifications of the portal vein, hepatic artery and hepatic duct, and are characteristic of the liver. The

as those from the capsular branches, become continuous, at the periphery of the lobule, with the intralobular capillaries which are derived from the branches of the portal vein.

Portal Vein.—The portal vein likewise enters at the transverse fissure, bringing to the liver the blood collected from the capillaries of the organs of digestion
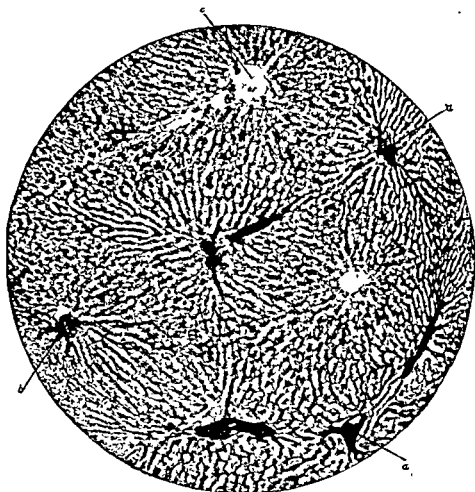
FIG. 398.—FROM A SECTION OF THE RABBIT'S LIVER WHOSE BLOOD VESSELS HAD BEEN INJECTED WITH A CARMINE-STAINED GELATIN MASS; SOMEWHAT MORE THAN A SINGLE LOBULE IS REPRESENTED.

a, interlobular veins, *b,* central vein; *c,* central vein from which the injection mass had fallen out, the capillaries are dark. Photo. ×70.

and absorption. It divides into numerous branches which follow the portal canals, in which they are known as the *interlobular veins,* and in this way reach all portions of the organ.

The interlobular veins throughout all their course give off small branches which at once enter the periphery of the hepatic lobules and immediately break into a brush of capillary vessels. These *intralobular capillaries (capilliform sinusoids)* converge toward the center of the lobule and anastomose to form a capillary

As has been pointed out by Mall (1906) the hepatic lobule cannot be regarded as the homologue of the lobule of other glands. For the portal canal with its bile duct, the excretory duct of the glandular unit, should be axial to the functional lobular unit. Moreover, an interlobular bile duct drains not the whole of a particular lobule, but portions of a number of adjacent lobules. The functional unit (portal lobule), in contradistinction to the structural unit (hepatic lobule) is accordingly that portion of liver tissue (portions of a number of hepatic lobules) supplied by an ultimate branch of the vessels of a portal canal. Thus a hepatic lobule is drained by several bile ducts, and conversely, a single ultimate bile duct drains portions of several hepatic lobules.

FIG. 396.—HUMAN LIVER CELL, SHOWING ENLARGED INTRACELLULAR CANALICULI, A CONDITION CHARACTERISTIC OF JAUNDICE. (Browicz.)

The liver secretes the bile—a fluid which aids in the digestion and absorption of fats—and in fact probably serves also an excretory rôle. Bile has a greenish-yellow color, due in part to the presence of the pigment bilirubin, which is believed to be identical with the hematoidin elaborated from the hemoglobin of the erythroplastids disintegrating in the spleen, and carried to the liver by way of the splenic and portal veins. Under certain pathological conditions known as jaundice, bile finds its way within the liver directly into the blood stream where it produces hemolysis of the red corpuscles. In addition to its bile-producing activity, the liver functions also as an organ of internal secretion, in the conversion of glycogen into sugar, the elaboration of urea, and the storage of a substance (hemopoietin) which prevents and cures pernicious anemia. Experimental evidence indicates that the liver is concerned greatly also with the production of fibrinogen by virtue of its extensive content of reticulo-endothelium, and with the conversion of fat into lecithin.

Blood Supply.—The liver is supplied with blood from two independent sources, the hepatic artery and the portal vein. That supplied by the artery is of minor importance and is destined only for the nutrition of the connective tissue framework of the organ.

On entering the liver at the transverse fissure, the *hepatic artery* gives off numerous capsular branches which ramify in the capsule of the liver and supply capillaries to its connective tissue. Other branches, the direct continuation of the hepatic artery, enter the portal canals and by repeated division form the *interlobular arteries,* which ramify in the tissue of Glisson's capsule, and whose vaginal branches supply capillaries to this connective tissue. These capillaries, as well
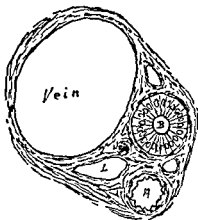
FIG. 397.—A PORTAL CANAL, INCLUDING A BRANCH OF THE PORTAL VEIN, HEPATIC ARTERY (A), HEPATIC (BILE) DUCT (B), LYMPHATIC (L) AND UNMYELINATED NERVE TRUNK.

extremely abundant and are in intimate relation with the hepatic cells, each cell coming into contact with four to six capillary vessels. About one-third of the blood in the body is estimated to pass through the liver per minute.

The course of the blood through the vessels of the liver will be readily appreciated by reference to the following table which indicates the succession of the hepatic blood vessels:

1. Portal vein	1. Hepatic artery
2 Interlobular veins	2. Interlobular arteries
3 Branches to lobule	3. Vaginal branches and capillaries in Glisson's capsule
	4. Intralobular capillaries
	5. Central vein (intralobular)
	6. Sublobular veins
	7. Hepatic veins
	8. Vena cava inferior

The three classes of veins, interlobular, central and sublobular, are readily differentiated by the fact that the two latter lie alone, while the interlobular veins are always in company with the ducts and arteries within the portal canals. Moreover the central vein has almost no connective tissue wall until near its exit from the lobule, where it passes into the sublobular branches. The sublobular veins, on the other hand, possess a relatively thick connective tissue wall and even some smooth muscle, except in the very smallest, which are to be regarded as mere interlobular continuations of central veins which soon unite to form the larger sublobular vessels.

FIG. 400.—INTRALOBULAR NERVE FIBERS IN A RABBIT'S LIVER.

a, hepatic cells; *b*, nerve fiber Golgi stain Highly magnified (Berkley.)

Lymphatics.—The lymphatics of the liver may be considered as consisting of a superficial set which supplies the hepatic peritoneum and the capsule of the liver, and which is continuous with a deeper set in Glisson's capsule. The lymphatics of the deep set begin as perivascular spaces within the lobule, from which the lymph enters larger lymphatic vessels in the interlobular connective tissue, which follow the vessels of the portal canals to their exit from the liver. The larger lymphatics pass to the abdominal lymph nodes. Other lymphatics follow the sublobular and hepatic veins and pass to the mediastinal lymph nodes.

Nerves.—The nerves of the liver are mostly of the unmyelinated variety. They follow the portal canals and are distributed to the walls of the blood vessels, the walls of the bile ducts, and to the capsule of the liver. Naked fibrils from these trunks also enter the lobules and form a plexus among the hepatic cells,[63] in relation with which they form fine terminal brushes and varicose end-knobs.[64]

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[63] Korolkow, 1893.
[64] Berkley, 1895

network, in the elongated meshes of which are the cords of hepatic cells. These capillaries approach the center of the lobule where they unite to form the intra-lobular or *central vein*. The central vein frequently begins in the form of a Y, its two or more branches finally uniting to form a single vessel which pursues its course through the axis of the lobule. The central vein makes its exit at the basal periphery of the lobule and enters the interlobular connective tissue where it unites with its fellows to form larger *sublobular veins*. The sublobular are easily distinguished from the interlobular veins by their thicker walls and by the fact that the former pursue an independent course through the tissue of Glisson's capsule, being nowhere in relation with either artery or duct.

FIG. 399—A GROUP OF SURFACE LOBULES ON THE PIG'S LIVER.
p. v., portal vein; *s. v.* sublobular (hepatic) vein; *c. v.*, central (hepatic) vein. ×10.
(F. P. Johnson)

The sublobular veins are, as a rule, vessels of considerable size, and by fre-quent union with their fellows become constantly larger. In their general direction they tend toward the dorsal surface of the liver and finally make their exit as four or five large *hepatic veins* which enter the inferior vena cava.

The blood supply of the liver, 3 to 54 per cent of which can be accounted for in the hepatic artery, 32 to 64 per cent in the portal vein,[62] is peculiar in that: (1) the greater portion of its blood has already passed through the capillaries of the digestive organs before entering the liver; (2) its arterial supply is relatively meager and supplies only the connective tissue framework, intermingling with the portal blood at the periphery of the lobule; (3) its intralobular capillaries are

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[62] Macleod and Pearce, 1914.

The blood vessels form a plexus just outside the muscular coat, from which branches are distributed to the peritoneal coat and to a plexus in the depth of the mucosa from which capillaries are supplied to the muscular layers and to a subepithelial plexus. The nerves are distributed to the blood vessels and to the muscular wall. Minute ganglia occur in the muscular coat.
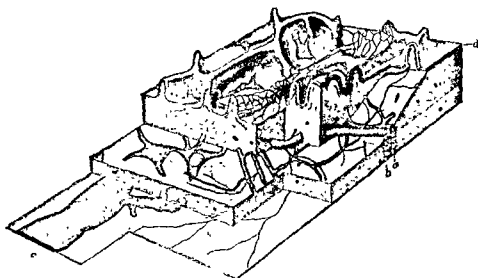
FIG. 402.—RECONSTRUCTION OF THE WALL OF A DOG'S GALLBLADDER.

a, vein; *b*, artery; *c*, lymphatic vessel; *d*, epithelium ×6o. (Sudler.)

The wall of the gallbladder may contain various epithelium-lined ducts and sinuses. These may extend peripherally as far as the subserous connective tissue. The ducts (true Luschka ducts) are interpreted as aberrant bile ducts and remnants of the embryonic tubular primordia of the liver. They are blind at both ends. The sinuses (Rokitansky-Aschoff) are deeper and wider outpouchings, probably the result of readjustments of the mucosa following prolonged overdistention of the gallbladder.[66]

The gallbladder is lacking in many species of vertebrates including the lamprey, pigeon, rat, horse, certain ruminants and the porpoise. In these instances a well-differentiated cystic primordium suffers regressive changes in later embryonic life and ultimately disappears. With the disappearance of the gallbladder, the biliary system generally undergoes compensatory enlargement. Dilatation of the bile ducts is frequently associated with congenital absence of the gallbladder, and commonly follows cholecystectomy.

THE LARGER BILE DUCTS

These include the cystic duct, the main hepatic duct, and the common bile duct. The histology of these ducts resembles that of the gallbladder, except that the muscularis forms a relatively less robust layer of smooth muscle cells, circu-

[66] Béla Halpert, 1927.

THE GALLBLADDER

The wall of the gallbladder consists of three coats: mucous, muscular and fibroserous. The mucous membrane is markedly folded or corrugated, the irregularly polygonal depressions being relatively broad at the fundus but becoming narrower toward the neck of the organ. The lining epithelium is of the tall columnar variety, with spheroidal or ovoid nuclei which lie near the base of the cell. The free extremity of the epithelial cells presents an indistinct cuticular border.
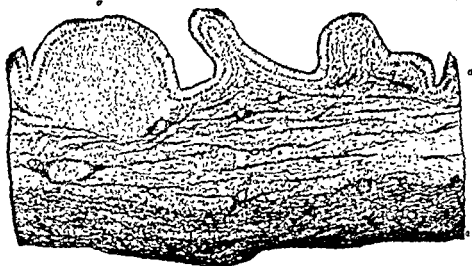
FIG. 401.—FROM A SECTION THROUGH THE WALL OF A DOG'S GALLBLADDER. *a*, epithelium; *b*, lymph nodule; *c*, serous coat. ×80. (Sudler.)

The epithelium follows all the folds of the mucosa and lines the intervening depressions.

The lamina propria of the mucosa consists of delicate connective tissue and contains a few smooth muscle fibers derived from the muscular coat. It is connected with the tunica muscularis by a thin layer of denser connective tissue which contains blood and lymphatic vessels and which simulates a submucosa.

The gallbladder possesses a distinct muscular wall, consisting of numerous interlacing smooth muscle bundles the most of which are circularly disposed. Occasionally they form fairly distinct circular and longitudinal layers.

The fibroserous coat consists of loose areolar tissue, which contains the larger blood vessels with which the organ is abundantly supplied. The free surface of the gallbladder also receives a peritoneal investment.

Occasional mucous glands occur in the mucosa of the gallbladder. These are mostly of small size and widely separated, but toward the neck of the organ they increase in both number and size. They form short, branched, convoluted tubules. The mucosa of the normal gallbladder secretes calcium in large amounts, cholesterol in negligible amounts.[65]

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[65] Dostal, Hrdina and Goff, 1932.

THE URINARY SYSTEM

This system includes the *kidneys,* which are two large bean-shaped glands, together with their excretory passages, the *ureters,* which conduct the urine to the *urinary bladder,* whence it is voided through the *urethra.*

THE KIDNEY

Each kidney is a gland of the compound tubular type, measuring about 4½ inches in length, 2½ inches in width, and 1½ inches in thickness. Its secretion, the urine, is produced by the *uriniferous* or *renal tubules,* which are long, tortuous canals beginning near the surface of the kidney and finally ending at the hilus of the organ where they pour their secretion into the calices of the renal pelvis. The uriniferous tubules are in intimate relation with the renal blood vessels which supply rich capillary plexuses to the entire extent of the tubules. Each uriniferous tubule consists of both tortuous and straight portions, and these are so regularly disposed as to produce macroscopical variations in the appearance of the different portions of the renal parenchyma according as the tortuous or the straight portions of the tubules predominate. These variations result in the following topographical subdivisions.

TOPOGRAPHY

If the kidney be divided parallel to its long axis by an incision extending from its convex surface to the hilus, the cut surface shows that the parenchyma is divisible into a superficial *cortex* and a central *medulla.* The slit-like hilus of the organ opens into a deep excavation, the *renal sinus,* which is occupied by the *renal pelvis* and its subdivisions, the *calices* and *infundibula,* into which the medulla projects in the form of several conical pyramids. The pelvis of the kidney, the expanded funnel-form beginning of the ureter, toward the renal parenchyma divides into two, sometimes three, major calices, which in turn subdivide into several minor calices or infundibula, each of which incloses the conical apex of a projecting medullary or *renal (malpighian) pyramid.*

Medulla.—The medulla of the kidney consists of a number of these conical renal pyramids (usually twelve to fifteen) each of whose apices, as already stated, is received into the extremity of a renal calix. Occasionally a calix may receive two papillae. The base of each pyramid is embedded in the adjacent renal cortex, and

larly disposed for the most part in the hepatic duct, longitudinally disposed as
scattered bundles in the cystic and common ducts. At the level where the common
bile duct enters the duodenum, the ampulla of Vater, the circular fibers are
increased to form a sort of sphincter (of Oddi). The mucosa of the cystic duct
is thrown into from five to twelve oblique crescentic folds, the "spiral fold."
These folds are similar to those of the neck of the bladder where they form
Heister's valve. They are remnants of a continuous "spiral valve" of fetal life,
and contain delicate strands of transverse and longitudinal smooth muscle cells.
In the mucosa of these ducts, especially numerously in that of the hepatic duct,
occur certain branched tubular gland-like structures, the "parietal sacculi" of Beale,
lined with tall columnar cells. These have long been designated as mucous glands,
but Sweet [47] interprets them as structures having an absorptive function similar to
that of the gallbladder lining, providing a mechanism for bile concentration and
for the transfer of bladder bile directly to the lymphatics.

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[47] Sweet, 1924.

as a portion of cortex inserted between the adjacent rays; (3) a narrow *boundary zone* of the cortex, "cortex corticis" of Hyrtl, which is included between the fibrous capsule of the organ and the tips of the cortical rays, and in which the renal corpuscles, though present, are relatively few in number.

FIG 404 —THE STRUCTURE OF THE KIDNEY.

a, papillary zone, and *b,* boundary zone of the medulla; *c,* cortex; *1,* apex of a renal pyramid; *2,* capsule, *3,* tubules of the medulla, *4,* vasa recta; *5,* vascular arcades; *6,* a cortical ray, *7,* labyrinth, *8,* interlobular artery, *9,* renal corpuscle, *10,* "cortex corticis." (Testut.)

Renal Lobule.—In fetal and infantile life the kidney is distinctly lobed. This condition is permanent in some animals—*e.g.,* reptiles, birds, porpoise, ox, bear—each lobe consisting of a renal pyramid with its related portion of cortical substance.

In man, after the first year, the renal lobes completely fuse and eventually leave scarcely a trace of the early lobed condition.

Internally this fetal lobed condition is in part indicated by the definitive renal pyramids, from eight to eighteen in number, each representing the product of fusion of from two to nine primitive lobes. In certain mammals—*e.g.,* mouse, rabbit, cat, guinea-pig—neither a primitive nor definitive internal or external lobar arrangement appears. Such kidneys are designated unipyramidal or unipapillary, in contradistinction to the multipapillary type. In certain of the perissodactyls (elephant, horse) no distinct pyramids are present.

that portion of the cortex which is interposed between the bases of adjacent pyramids, and thus brought into relation with the fibrous and adipose tissue which envelops the pelvis and calices at the hilum of the organ, composes the cortical *renal columns* (of Bertin).

Each renal pyramid may be subdivided into a central free portion, the apical or *papillary* zone of the medulla, which is received into a calix, and an outer or basal portion, which is embedded in the renal cortex and is known as the *boundary zone*

Fig. 403—Longitudinal Section of Kidney.

1, cortex; *1'*, cortical rays; *1''*, labyrinth; *2*, medulla; *2'*, papillary portion of medulla; *2''*, boundary layer of medulla; *3*, transverse section of tubules in the boundary layer; *4*, fat of renal sinus; *5*, artery; ***, renal column of transverse medullary rays; *A*, branch of renal artery; *C*, renal calix; *U*, ureter (After Tyson and Henle, from Hill.)

of the medulla. These two portions of the medulla, the papillary and boundary zones, can be readily distinguished, since the latter contains only narrow tubules and is highly vascular, while the former, relatively deficient in blood vessels, contains the broad termination of the uriniferous tubules, the *papillary ducts* (of Bellini) which converge toward the apex of the pyramid where they open into the calices.

Cortex.—The cortex of the kidney, on careful observation, presents numerous dark lines or delicate columns which radiate from the base of the pyramids outward toward the surface of the organ. These radiating columns are the *medullary rays* (pyramids of Ferrein) or *pars radiata* of the cortex. They contain straight portions of the uriniferous tubules; these are continuous with the similar tubules in the boundary zone of the medulla. These columns lie within the cortex and not, as their name might be taken to indicate, in the medulla. They are termed "medullary rays" because of their peculiar relation to the medulla, from which they extend outward in a radial direction. It would seem more proper to designate them "cortical rays."

That portion of the cortex which invests the cortical rays and which includes all the remaining cortical portions of the organ, consists of extremely tortuous tubules, and is characterized by the presence of small globular bodies, each of which contains a tuft of capillary vessels. These are the *renal corpuscles* (malpighian bodies) which are characteristic of the kidney. The portion of the cortex in which they occur includes the entire cortical substance with the exception of the cortical rays, and is known as the renal *labyrinth* or *pars convoluta*. The labyrinth is divided into: (1) the *renal columns*, already mentioned; (2) the intercolumnar portions, or *labyrinth proper*, which includes that portion of the labyrinth which invests the cortical rays, and which, in sections cut parallel to these columns (longitudinal sections) appears

as a portion of cortex inserted between the adjacent rays; (3) a narrow *boundary zone* of the cortex, "cortex corticis" of Hyrtl, which is included between the fibrous capsule of the organ and the tips of the cortical rays, and in which the renal corpuscles, though present, are relatively few in number.

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FIG. 403—LONGITUDINAL SECTION OF KIDNEY.

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tissue is slightly increased in amount about the larger blood vessels, the renal corpuscles of the cortex, and the small blood vessels of the boundary zone of the medulla. At the apex of the renal pyramid it invests the large papillary ducts in considerable quantity.

URINIFEROUS OR RENAL TUBULES

The uriniferous tubules begin in the cortical labyrinth as the capsules of the renal corpuscles. Assuming a tubular form they then pursue a tortuous course through the *pars convoluta* and finally enter the boundary zone of the medulla,
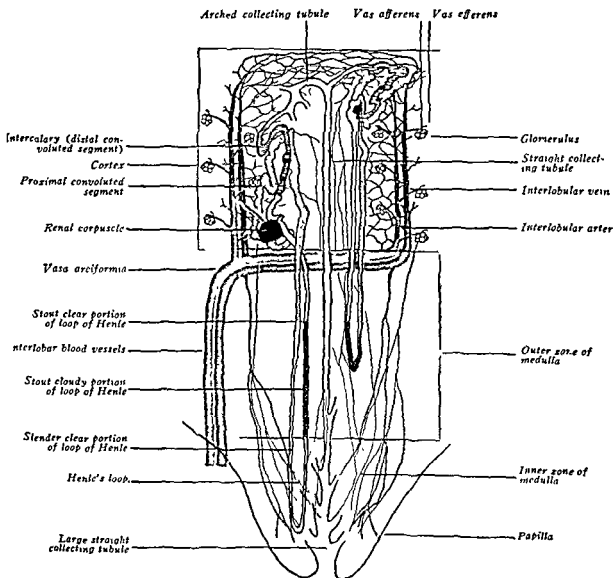
FIG 406—URINIFEROUS TUBULE OF A MAMMAL.
(Adapted from Peter and Merkel.)

Here, much reduced in size, they form the loop of Henle, which consists of a short, descending, slender limb, a U-shaped loop, and a long, ascending or stout limb. This last division, after recrossing the boundary zone of the medulla, enters a *pars radiata*

The term renal lobule or *renculus*, as applied to the adult human kidney, refers to a still smaller subdivision of the organ, one which includes a single cortical ray together with that portion of the cortical labyrinth by which it is immediately invested. Its peripheral boundary is marked by the interlobular blood vessels. This lobule is the anatomical unit of the kidney and is thus comparable to the portal and to the pulmonary lobule, except that its arterial supply enters at the periphery. The tortuous secreting portions of its uriniferous tubules are contained in the labyrinth at the periphery of the lobule, while its straight conducting portions lie in the cortical ray in the axis of the lobule. The larger interlobular arteries and veins lie at the periphery, where they supply branches to several adjacent lobules.

RENAL CONNECTIVE TISSUES

The kidney is enveloped by a fibrous *capsule*, the *tunica fibrosa*, which is loosely attached to the substance of the organ and contains the usual proportion of elastic fibers together with a little smooth muscle. A fatty layer, the *tunica adiposa*, invests the capsule. At the hilus of the organ the capsule is continuous with the connective tissue which envelops the renal pelvis, calices, and infundibula, and which, in the intervals between adjacent infundibula, comes into relation with the cortical substances of the renal columns.

This connective tissue of the hilus is of the areolar variety and contains much adipose tissue. It supports the large arteries and veins as they pass along the surface of the renal pelvis on their way to and from the renal columns, where they enter or leave the parenchyma. Sympathetic nerve fibers and a few small ganglia are also found in this region.

The connective tissue of the interior of the organ, *interstitial tissue*, is very scanty, and in most parts consists only of isolated fibrils which invest the blood vessels and the renal tubules. It forms a very delicate reticulum by which the walls of the uriniferous tubules are loosely united. If the epithelium of these tubules is removed, a delicate fibrous network remains; this network incloses a homogeneous basement membrane upon which the lining epithelium rests. Elastic fibers scarcely occur among the tubules of the kidney. The interstitial

FIG. 405.—RENAL TUBULE OF *ADULT RABBIT*, COMPLETELY ISOLATED BY TEASING.

Col. T., cortical collecting tubule ; Con. T., initial collecting tubule ; Med. L, medullary (Henle's) loop; Prox. Con., proximal convoluted segment ; Prox Con. Med S, proximal convoluted, medullary segment; Rc., Renal corpuscle; Th. Seg. L., thin segment of loop of Henle; Thi. Seg. Med L., thick segment of loop of Henle. (From Huber in Cowdry's *Special Cytology*, Paul B. Hoeber, Inc., New York.)

The glomerulus is a true arterial *rete mirabile*, since it receives an afferent arteriole, which, after contributing the capillaries of the glomerulus, passes out as an efferent arteriole again to enter a capillary plexus about the neighboring tubules of the renal cortex. The afferent vessel is of somewhat larger caliber than the efferent—a noteworthy fact because of its relation to the intraglomerular blood pressure.

On entering the glomerulus the arteriole divides into two vessels which immediately subdivide with the formation of five branches. Each of these branches forms a series of anastomosing capillary loops, from 30 to 45, whose convexity

FIG. 407A.—RENAL CORPUSCLE, DIAGRAMMATIC.

(After von Möllendorf.)

is directed away from the entering arteriole. The capillary loops reunite, in a similar manner, to form the efferent vessel, which leaves the glomerulus in company with the afferent; but, once-out, they soon part company, the efferent vessel breaking into a second capillary plexus about the neighboring tubules. Within the glomerulus the capillaries are united by a very delicate but scanty connective tissue containing no elastic fibers.

Attention has recently been directed to a group of afibrillar smooth muscle cells

and returns to the region of its origin, where it becomes again convoluted. A short *arched tubule* connects this convoluted portion with a *straight collecting tubule* of the cortical ray. The collecting tubules traverse the whole length of the ray, uniting with their fellows and receiving other arched tubules along their entire course. They then cross the boundary zone of the medulla, and finally in the papillary zone, having meanwhile received numerous accessions of straight collecting tubules, form the large terminal tubules, the papillary ducts, which pour the urinary secretion into the renal calices.

Each uriniferous tubule may thus be subdivided into several portions which differ from each other, not only in their location, but also in the character of their lining epithelium. The successive portions which compose a single uriniferous tubule may be enumerated as follows: (1) capsule of the renal corpuscle, (2) neck of the tubule, (3) proximal convoluted portion or tubule, (4) descending limb of Henle's tubule, (5) loop of Henle, medullary loop. (6) ascending limb of Henle's tubule, (7) distal convoluted portion or tubule, (8) arched collecting tubule, (9) straight collecting tubule and (10) papillary duct.

It should be borne in mind that all of these several portions form only successive parts of a single uriniferous tubule. Those portions of the urine which are secreted into the capsule of the renal corpuscle must therefore find their way through each of these successive portions before it can reach the excretory passages of the renal calices, pelvis, and ureter.

Renal Corpuscle (Malpighian Body).—A renal corpuscle consists of a spherical tuft of capillary vessels, the *glomerulus*, which in the course of its development

is invaginated into the end of the uriniferous tubule, and thus comes to be enveloped by a double layer of flattened epithelial cells known as the glomerular *capsule of Bowman.*

The inner visceral layer of the capsule closely invests the entire surface of the glomerulus, except at that point where the afferent and efferent vessels enter and leave the capillary tuft. At this point the visceral epithelium is reflected outward and becomes continuous with the parietal layer. The surfaces of these two layers are almost in apposition. The narrow interval between them which results from the slightly eccentric position of the glomerulus forms the first portion of the lumen of the uriniferous tubule. At that pole of the renal corpuscle which is opposite the entrance of its blood vessels the capsule opens, through a narrow neck, into the first or proximal convoluted portion of the uriniferous tubule.

FIG 407 —RECONSTRUCTION OF A GLOMERULUS OF THE HUMAN KIDNEY.

a, afferent arteriole; *b,* efferent arteriole; *c,* capillaries. × 444. (Johnston)

The glomerulus is a true arterial *rete mirabile*, since it receives an afferent arteriole, which, after contributing the capillaries of the glomerulus, passes out as an efferent arteriole again to enter a capillary plexus about the neighboring tubules of the renal cortex. The afferent vessel is of somewhat larger caliber than the efferent—a noteworthy fact because of its relation to the intraglomerular blood pressure.

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Attention has recently been directed to a group of afibrillar smooth muscle cells

in the media of the vas afferens, close to the glomerulus, designated the "juxta-glomerular neuro-myoarterial apparatus." [1] It is interpreted as an endocrine tissue whose secretion is believed to regulate the tonus of the renal arteriole. These cell groups are said to have a "glandular cycle culminating in the formation of acidophil or basophil secretion granules intermingled with minute vacuoles." *Experimental constriction of the left renal artery in the rabbit results in a hyperplasia of the*

FIG. 408—FROM THE CORTICAL LABYRINTH (PARS CONVOLUTA) OF THE HUMAN KIDNEY.

A large renal corpuscle is in the center of the figure. At its upper border are several sections of distal convoluted tubules The great majority of the tubules shown are from the proximal convoluted portions. *a*, a portion of a glomerulus; *b-b*, parietal layer of the capsule; *c*, proximal convoluted tubules, *d*, just within this point is a transection of a junctional tubule having relatively low and clear epithelium and a broad lumen. Hematein and eosin. Photo. ×135.

afibrillar cells of the vas afferens, occasional protrusion of groups of these cells into the glomerular tuft of capillaries, and a transformation of ordinary smooth muscle cells into afibrillar cells.[2]

The normal kidney of man from birth to forty years of age is said to contain from 800,000 to 1,000,000 glomeruli.[3] The two kidneys of the same individual

[1] Goormaghtigh, N. and Handovsky, H., 1938. [2] Goormaghtigh, N., 1939; [3] Moore, 1931.

contain approximately an equal number of glomeruli. In old age many glomeruli disappear; in the seventh decade the number of glomeruli equals two-thirds to one-half the adult count. The glomeruli have an average diameter between 150 and 200 microns.

The visceral layer of the capsule is firmly adherent to the walls of the glomerular capillaries. It consists of a single layer of flat epithelial cells which are intimately
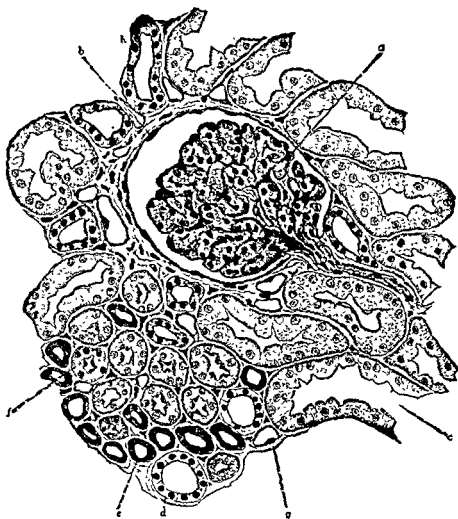
FIG. 409—FROM THE CORTEX OF THE HUMAN KIDNEY, SHOWING A TRANSECTION OF A CORTICAL RAY IN THE LOWER LEFT-HAND CORNER.

a, glomerulus; b, glomerular capsule; c, proximal convoluted tubule; d, collecting tubule; e, ascending limb of Henle's tubule; f, spiral tubule; g, blood vessel; h, distal convoluted tubule. Hematoxylin × 200 (After Schaper, from Stohr.)

blended with each other and with the endothelium of the capillaries. The epithelial cells possess a clear cytoplasm and a flattened ovoid nucleus, which, being thicker than the body of the cell, produces a considerable bulging. In fetal and infantile life the shape of the cells of this layer is cuboidal or even low columnar, but

becomes more and more flattened as development *progresses, until the epithelium* finally simulates a layer of endothelial cells.

The epithelium of the parietal layer is also cuboidal in fetal life, but during development becomes nearly as much flattened as that of the visceral layer. Its single layer of finely granular cells forms a complete lining for the capsule. It rests upon a homogeneous basement membrane which is invested by a thin layer of connective tissue. This fibrous layer is rather more highly developed about those renal corpuscles which lie near the medulla than about those of the more peripheral portions of the cortex.

Neck of the Tubule.—In this portion of the renal tubule the flattened epithelium of the glomerular capsule rapidly changes to the low columnar type of the proximal convoluted portion. This section is extremely short; it forms a constricted portion which marks the beginning of the tortuous tubule. This constriction is more apparent than real, since the caliber of the tubule in the neck is as great as in the succeeding portion whose external diameter is, however, much increased by the increasing height of the epithelial cells. This portion of the tubule being in relation with the renal corpuscle, is necessarily found in the cortical labyrinth.

Proximal Convoluted Portion.—This is the longest and broadest portion of the uriniferous tubule. Collectively the convoluted tubules form the *greater part of the cortical labyrinth*, in which region only they occur. This portion of the tubule is remarkable for the irregularity of its course, it being twisted and bent upon itself in a most tortuous manner. Arising at the renal corpuscle, it at first passes toward the surface of the organ, but soon turns about and runs toward the

Fig. 409A —Afferent Glomerular Arteriole in Longitudinal Section

This shows, on either side, a group of modified

adjacent to the glomerulus

medulla, at first with extreme convolutions, but later pursuing a rather spiral course (*spiral tubule*). At some distance beyond the border of the medulla the tubule becomes sharply constricted and enters the medullary boundary zone as the slender descending limb of Henle's loop.

The epithelium of the convoluted tubule is of the columnar or pyramidal type, its cells having broad, firmly united bases and conical free apices. The lateral margins of the cells are often so intimately blended at the base as to resemble a syncytium. When isolated, or if outlined by impregnation with silver salts, the borders of the epithelial cells are extremely irregular and are deeply fluted or serrated, the serrations of each cell interdigitating with those of its neighbors. The deep fluted serrations of the interlocked epithelium give many of its cells a coarsely striated appearance, the striation being more prominent beneath the centrally situated nucleus than in the apical portion of the cell. Other longitudinal striations in the proximal or basal portion of the cell are the result of a linear arrangement
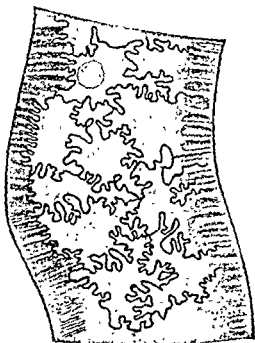
IG. 410.—FROM A LONGITUDINAL SECTION OF A CONVOLUTED TUBULE OF THE GUINEA-PIG'S KIDNEY.

The cell outlines have been blackened by the Golgi method Very highly magnified (Landauer)
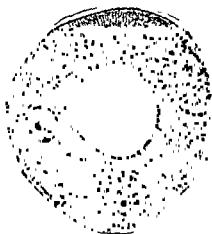
FIG 411.—CROSS-SECTION OF A PROXIMAL CONVOLUTED TUBULE FROM THE KIDNEY OF A MOUSE, SHOWING BASAL FILAMENTS (PROBABLY LARGELY MITOCHONDRIAL) BREAKING UP INTO GRANULES CENTRALLY, AND THE CENTRAL STRIATED BORDER OF THE CELLS.

Meves' mitochondrial technic. ×1000

of granules and filaments which occur in this part These appearances often give the epithelium of the convoluted tubules a peculiar striated or "rodded" character. The granules and filaments are probably largely mitochondrial in nature.

The apices of the epithelial cells are very easily destroyed, but when perfectly preserved often present a delicately striated border (brush border, stereocilia). The remaining portions of the cytoplasm are finely granular.

The nuclei of the epithelial cells of the convoluted tubules are spherical in shape and do not stain very deeply with nuclear dyes as compared with the more distinct and deeply staining nuclei of the collecting tubules. Thus they appear as if partially clouded by the granular cytoplasm, an appearance which is greatly exaggerated with the onset of acute inflammatory processes, which, on attacking the kidney, are prone to involve the convoluted tubules. The chromatin is quite evenly distributed throughout the nucleus and the nuclear membrane may be indistinct.

The cells of the proximal convoluted tubules are relatively rich in mitochondria, a condition suggesting a relatively high degree of activity. The extreme rarity of mitoses in these cells suggests a relatively long life tenure. In certain cases of nephritis, where large portions of the kidney have disintegrated, the proximal convoluted segments may undergo extensive compensatory hyperplasia.

The lumen of the proximal convoluted tubule is of variable caliber; it presents frequent dilatations. The caliber also depends, to some extent, upon the functional activity of the epithelium, whose cells become shrunken, and the lumen correspondingly dilated, during active secretion. The outside diameter varies from 40 to 60 microns, the diameter of the lumen from 15 to 25 microns. The length of this portion of the renal tubule is about 15 mm. The combined area of 1,000,000 proximal convoluted tubules of the human kidney is approximately 1 square meter.

While Heidenhain maintained that the production of urine was a secretory process entirely, the more generally accepted interpretation regards the process as in major part excretory. Bowman (1842) held the position that the glomerulus served as a filter for water and that the other constituents of the urine (urea, uric acid, sugar, creatinine and certain salts) were secreted by the activity of the epithelial cells of the renal tubule. Ludwig (1844) believed that the glomerulus acted as a filter to remove from the plasma, water and all substances other than protein; and that the filtrate was concentrated in the tubules by return of water to the blood by diffusion. The currently prevailing interpretation is in terms of the theory of Cushing (1926) which postulates simple filtration by the glomeruli and selective reabsorption of water and certain other constituents by the tubules.

That the glomerulus is not absolutely essential for the formation of urine seems indicated by the fact that in certain fishes (e.g. toad-fish, Edwards, 1928) the kidney (mesonephros) lacks glomeruli but nevertheless forms urine. In these fishes each nephron consists of a segment analogous to the proximal convoluted tubule of mammals; and these aglomerular kidneys produce typical urine. The kidney functions largely as a regulator of water metabolism, mediated in part especially by the thin segment of the loop of Henle, where water is resorbed under the control of pitressin, a hormone of the posterior lobe of the pituitary gland.

Descending Limb of Henle's Tubule.—In this portion (the slender or narrow tubule of Henle), which is, typically, located in the boundary zone of the medulla, the uriniferous tubule becomes very much narrowed (8-15 μ). The decreased

diameter is the result of diminished height of the lining epithelium rather than of any change in the caliber of the tubule. The length of this portion of the tubule is very variable; typically it corresponds very nearly with the breadth of the medullary boundary zone.

The lining epithelium of the descending limb is of a peculiar flattened variety. Its cells possess an ovoid nucleus which, being thicker than the surrounding portions of the cell, projects slightly into the lumen of the tubule. The bulging nuclei of opposite sides of the tubule are not in apposition but interlock with one another, the nuclei of one side of the tubule being opposed to the cell margins of the opposite side. The lumen of longitudinal sections through the axis of the tubule thus acquires a sort of zigzag outline. The nuclei stain deeply and possess an evenly distributed chromatin. The cytoplasm of the epithelium is very finely granular, and although its cells are intimately adherent at their lateral margins they do not present the typical striations which are characteristic of the preceding portion of the epithelium. Reabsorption of water is active in this portion.

Loop of Henle.—As the descending limb enters the loop of Henle, the tubule makes an abrupt turn and returns toward the cortex. The location of the loop, being dependent upon the variable location in the cortex of the renal corpuscle and the variable length of the slender segment, may be in any portion of the medulla except the extreme tip of the pyramids. Its most frequent site is near the junction of the boundary and papillary zones.

The structure of the loop may be that of either the descending or the ascending limb of the typical loop. It is also subject to great variations, since the change in structure from the narrow to the broad type, though it typically occurs just prior to the formation of the loop, is frequently delayed until well into the ascending limb. As a rule, the change in type occurs earlier when the loop lies in the boundary zone, and later when it occurs nearer the apex of the renal pyramid. The stout ascending limbs do not occur in the papillary zone of the medulla.

Ascending Limb of Henle's Tubule.—This portion of the tubule (the broad or stout limb) returns through the boundary zone of the medulla and enters a cortical ray, its course being parallel to that of the descending limb. It then passes toward the surface of the kidney, but finally leaves the ray and enters the labyrinth to reach that renal corpuscle (close to the vas efferens) from which the uriniferous tubule took origin, and in relation to which the tubule again acquires a tortuous course (distal convoluted portion). Within the boundary zone of the medulla this portion of the tubule is much broader than the preceding division, but it becomes somewhat reduced in size in its course through the cortical ray. These cells do not have brush borders.

The epithelium of the ascending limb is of a short cuboidal form. Its cytoplasm resembles that of the lining epithelium of the convoluted portion, although the nuclei in the tubule of Henle are rather more distinct. Basal striations are also less distinct than in the convoluted tubule, the lateral serrations less deep, and the cell outlines sharper. The cells of this portion frequently possess a slightly imbricated arrangement. The average length of the tubule (medullary loop) is 15 mm.

The comparative studies of mammalian kidneys by Peter [4] have revealed certain important details. Peter divides the medullary portion of the renal pyramid into an *outer* and *inner zone;* these portions have no precise correspondence with the boundary and papillary zones above mentioned. In the outer zone Peter describes an *outer* and an *inner stripe,* the line of demarcation being the very definite level where the proximal convoluted tubule passes into the thin, clear, narrow limb of Henle's loop (Fig. 406). The point of transition from outer to inner *zone* is

Fig. 412.—A Group of Tubules from a Transection of a Renal Pyramid of the Human Kidney; the Section Passes through the Boundary Zone.

a, collecting tubule; *b,* ascending limb of Henle's loop; *c,* descending limb; *d,* loop of Henle. Hematein and eosin. Photo. ×275.

marked by a change in the character of the epithelium lining the distal limb of the long Henle's loops; the epithelium becomes cloudy (granular) and thicker. In view of the great variability in the character of the epithelium at the various levels in loops of different lengths, and the recognition by Peter of a thicker cloudy segment, it seems better to speak of *slender clear, stout clear,* and *stout cloudy segments of the loop (tubule).* In kidneys of the dog and cat there are no really short loops, none lying within the outer zone. In the kidney of the pig many loops lie in the cortex; such loops lack entirely the slender, clear narrow limb.

Distal Convoluted Portion.—This portion of the uriniferous tubule (intercalary or intermediate portion) begins close to the vascular pole of the renal corpuscle, and, after several irregular contortions which are confined to the region

4 Peter, 1909

of the cortical labyrinth, enters an arched collecting tubule. The distal is much shorter than the proximal convoluted portion. Its caliber is subject to great irregularities, so much so that its early turns have been characterized as the irregular or zigzag portion of the uriniferous tubule. The epithelium of this section resembles that of the proximal convoluted portion but is lower, more cuboidal, the striations are indistinct, and the cells lack brush borders.

This portion terminates the typically *secretory section of the uriniferous tubule.* This secretory segment is termed the *nephron.* Beyond here the tubule possesses more the function of a duct, hence its epithelium shows a decided change in character. Hitherto it has possessed the peculiar character, the typically granular cytoplasm, of a secreting type of cell. Beyond the terminal secretory portion or nephron the epithelium is no longer so granular but possesses a characteristically clear appearance. The secretory and excretory portions of the renal tubule have a separate embryonic origin, and only secondarily unite to form a continuous duct.

Arched Collecting Tubule.—The arched collecting tubule (junctional tubule) is a short portion of the uriniferous tubule which connects the distal convoluted portion in the cortical labyrinth with the straight collecting tubules of the cortical rays. Its course is *characteristically arched.*

The epithelium of the arched tubule consists of clear cuboidal cells with distinct outlines and deeply stained, sharply defined nuclei. The chromatin of the nucleus is irregularly distributed, forming numerous karyosomes, and the nuclear membrane is distinct. The cytoplasm is relatively devoid of granules, and unlike that of the secreting epithelium does not possess a strong affinity for the acid dyes.

Straight Collecting Tubules.—These portions of the renal tubules begin in the cortical rays, where they receive the arched tubules, and, proceeding to the medulla, become considerably increased in size. They penetrate the boundary zone of the medulla, all pursuing a parallel or slightly convergent course, and occasionally uniting with each other. On entering the papillary zone, by frequent union they become rapidly larger, and in the apex of each pyramid finally form about a score of large terminal papillary ducts. Though shorter than the convoluted tubules, the straight collecting portions, because of their direct course, traverse a broader area of the renal tissue. Beginning near the peripheral end of the cortical rays, in these columns they cross nearly the whole breadth of the renal cortex and entering the medulla extend from base to apex of the renal pyramid.

Throughout their whole course they progressively increase in size and caliber. A corresponding progressive increase in the height of their epithelial cells likewise occurs, so that the lumen of the straight tubules of the medulla is not only actually greater than that of those of the cortical rays, but the walls of the former tubules are also considerably thicker. The extreme of this progression is found in the broad lumen and tall epithelium of the papillary ducts.

The epithelium of the straight tubules, like that of the arched, possesses a clear cytoplasm, distinct and deeply staining chromatic nuclei, and well-defined cell outlines. Beginning in the cortical rays with a low columnar type, it gradually increases in height in the course of the tubule until, in the *papillary zone,* the

The comparative studies of mammalian kidneys by Peter [4] have revealed certain important details. Peter divides the medullary portion of the renal pyramid into an *outer* and *inner zone;* these portions have no precise correspondence with the boundary and papillary zones above mentioned. In the outer zone Peter describes an *outer* and an *inner stripe,* the line of demarcation being the very definite level where the proximal convoluted tubule passes into the thin, clear, narrow limb of Henle's loop (Fig. 406). The point of transition from outer to inner *zone* is

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a, collecting tubule; *b,* ascending limb of Henle's loop; *c,* descending limb; *d,* loop of Henle. Hematein and eosin. Photo. ×275.

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─────────

[4] Peter, 1909

Medulla
{
A. Outer Zone
{
1. Outer stripe
   (a) straight collecting tubules
   (b) proximal convoluted tubules
   (c) stout ascending limbs of Henle's loops, including both
      (x) stout cloudy portions, and
      (y) stout clear portions

2. Inner stripe
   (a) slender clear descending limbs of Henle's loops
   (b) stout cloudy portion of ascending limbs of Henle's loops
   (c) short loops of Henle, of stout cloudy type of epithelium

B. Inner Zone
   (a) straight collecting tubules
   (b) long loops of Henle, entirely of slender clear type
}

The following tabular résumé may be of service by emphasizing the more important peculiarities of the several portions of the uriniferous tubule.

Portion of Tubule	Epithelium	Location
Renal corpuscle...	Flattened, endothelioid	Cortical labyrinth
Neck	Changing from flattened to low columnar	Cortical labyrinth
Proximal convoluted	Low columnar, granular, and rodded	Cortical labyrinth
Spiral portion of above.. ..	Low columnar, granular, and rodded	Cortical rays
Descending limb	Low cuboidal or flattened, granular	Medulla (boundary and papillary zones)
Loop	Varies; like either the preceding or following	Medulla (boundary and papillary zones)
Ascending limb	Cuboidal or low columnar, granular, imbricated	Boundary zone of medulla and cortical rays
Distal convoluted	Low columnar or pyramidal, granular, and rodded	Cortical labyrinth
Arched collecting	Cuboidal, clear cytoplasm, dark nucleus	Cortical labyrinth
Straight collecting	Cuboidal, changing to columnar	Cortical rays and both zones of medulla
Papillary duct	Cuboidal, tall columnar	Papillary zone of medulla

RENAL BLOOD VESSELS, LYMPHATICS AND NERVES

Blood Supply.—The kidney receives its blood supply from the renal artery, which, as it enters the hilus, divides into two sets of principal branches, of which the ventral set supply three-fourths, the dorsal set one-fourth of the renal substance. These principal branches, the *arteriae propriae renales*, or interlobar arteries, are embedded in the connective tissue of the sinus and follow the walls of the

epithelium acquires a tall columnar form. The clear cytoplasm and distinct nuclear membranes of the epithelium of the collecting tubules stand out in sharp contrast to the granular cytoplasm and the evenly distributed chromatin in the nuclei of the lining cells in the secreting portions of the uriniferous tubules.

Papillary Ducts.—These ducts of Bellini are the wide mouths of the uriniferous tubules which are formed by the dichotomous union of from ten to thirty collecting tubules, and which empty their secretion into the renal calices at the apex of the renal pyramids. They attain a diameter of from two hundred to three hundred microns. They are lined by tall columnar cells with an exceptionally clear cytoplasm which has an affinity for the basic in preference to the acid class of dyes. The nuclei are spheroidal or ovoid in shape and lie in the basal portion of the cell. At their termination several papillary ducts frequently open into a common depression or foveola which is lined by an involution of the layer of transitional epithelium, derived from that of the renal calix, by which the free papillary portion of the renal pyramid is clothed.

It is obvious that the entire renal tubule, from the glomerular capsule to the papillary duct, is a continuous canal whose epithelial wall, supported by a thin homogeneous basement membrane varies in character in each succeeding portion. Thus the proximal and distal convoluted portions and the typical ascending limbs of Henle's loops possess a granular, rodded or striated, acidophil, secreting epithelium; the capsule has thin cells of an endothelioid type. The typical descending limb and loop of Henle's tubule are lined with flattened finely granular and faintly acidophil epithelium; the curved and straight collecting tubules and papillary ducts possess a clear columnar epithelium. It should also be noticed that the several portions of the renal tubule occur in different topographical subdivisions of the kidney and that, therefore, each of the subdivisions contains only certain characteristic portions of the renal tubule. Thus

Cortical Labyrinth (*Pars Convoluta*)	Renal corpuscle Neck of the tubule Proximal convoluted portion Distal convoluted portion Arched collecting portion
Cortical Rays (*Pars radiata*)	Spiral portion of the convoluted tubule Ascending limb of Henle's tubule Straight collecting portion
Boundary Zone of the Medulla	Descending limb of Henle's tubule Ascending limb of Henle's tubule Straight collecting portion
Papillary Zone of the Medulla	Descending limb of Henle's tubule Loop of Henle's tubule Straight collecting portion Papillary duct

The following outline, based upon the investigations of Peter, gives a more detailed classification of the different portions of the renal tubule in the medulla:

straight course between the parallel tubules of this region and are known as *arteriolae rectae*. They branch freely at acute angles and form a rich capillary plexus in the boundary zone, the longest of the vessels reaching beyond the limits of this region to supply a less abundant plexus to the papillary zone of the medulla.

FIG. 414—ARTERIAL SUPPLY OF KIDNEY.

The arteriolae rectae arise exclusively as branches of efferent arterioles from glomeruli of the corticomedullary zone. (Morison.)

The medullary capillaries, like those of the rays in the cortex, form a network with elongated meshes which surround the parallel tubules of this region. The capillaries of the cortical labyrinth, being distributed among irregular tortuous tubules, possess a more polygonal mesh.

The interlobular veins begin near the surface of the organ where small venules, derived from the cortical capillaries and from occasional anastomoses with the capsular vessels, unite to form broad thin-walled venous spaces, the *stellate veins* of Verheyn, just beneath the capsule. From these subcapsular vessels the interlobular veins arise, and pass toward the medulla in company with the interlobular arteries, throughout their course collecting the minute venules which return the blood from the capillaries about the tubules of the renal cortex.

Arriving at the border of the medulla, but still embedded in the cortical substance, the interlobular veins turn sharply, at nearly right angles to their former course, and by free anastomoses form a *venous arcade* (arciform vein). This arcade receives the *venulae rectae* coming from the capillary plexuses of the

calices and infundibula, upon which they lie, thus reaching the renal columns between the renal calices. Here they enter the cortical substance and divide, each branch passing in a curved or arched manner beneath the base of the adjacent pyramids. These vessels form an incomplete arterial arcade (arciform artery) which lies in the margin of the cortex at the outer border of the medullary boundary zone.

From the arterial arcade, branches are supplied only to the cortical substance. These cortical branches of the arterial arcades are vessels of considerable size which enter the labyrinth between the cortical rays and as *interlobular arteries* (cortical arterioles) pass through the surface of the organ, a few of the longest branches reaching the fibrous capsule with whose vessels they anastomose. Throughout their whole course the interlobular arteries give off numerous short branches, which leave the parent stem at a wide angle, and pass directly to a renal corpuscle as the *afferent artery* (arteriole; vas afferens) to its glomerulus. Here it supplies the capillary plexus in the manner already described (p. 404).

FIG. 413—THE DISTRIBUTION OF THE LEFT RENAL ARTERY.

Of the six arteriae propriae renales, five enter in front of the renal pelvis, and, lying upon the wall of the calices, are distributed from the arterial arcade to the cortex *a*, ureter; *b*, renal artery; *c*, arteriae propriae renales; *d*, the dark border is the cortex, within which is the lighter medulla. (After Brodel, from Szymonowicz and MacCallum)

Certain of the afferent arterioles are peculiar in that (1) they give off small branches which supply capillaries directly to the convoluted tubules of the cortical labyrinth; and (2) they occasionally form a small rete mirabile before they reach the glomerulus. By far the greater portion of the branches of the interlobular arteries, however, pass directly to the glomeruli. The capillaries of the glomerulus reunite to form an efferent vessel which, after leaving the corpuscle, promptly breaks into a second capillary plexus about the adjacent tubules.

The medulla receives its arterial supply from efferent vessels of those glomeruli which lie in the juxtamedullary portion of the cortex.[5] These medullary arterioles are peculiar in that they lack circular muscle fibers; structurally they resemble the medullary veins. They are slender vessels which pursue a characteristically

[5] Morison, 1926

The deep renal lymphatics accompany the arteries and veins throughout their course. They form narrow cleft-like vessels of irregular caliber in the scanty interstitial tissue between the uriniferous tubules of both cortex and medulla. These vessels are relatively few in number. They converge to the hilus of the organ where they pass to the nearby lymphatic nodes.

Nerves.—The nerves of the kidney include both myelinated and unmyelinated fibers. The sympathetic fibers form a ganglionated plexus in the connective tissue about the renal pelvis. From this plexus fibers are distributed to the blood vessels of the capsule and to the parenchyma of the organ. The latter accompany the blood vessels, distributing their fibers to the walls of the arteries and veins and also to the uriniferous tubules of both the cortex and medulla.

The parenchymal branches form an epilemmal plexus in the interstitial connective tissue about all portions of the uriniferous tubule. From this plexus fibrils pierce the membrana propria and anastomose to form a hypolemmal plexus about the base of the epithelial cells. Terminal fibrils penetrate between the epithelial cells where they form minute end-knobs.

FIG. 415.— NERVE ENDINGS IN A CONVOLUTED TUBULE OF THE FROG'S KIDNEY

a, nerve fiber; *b*, blood vessel; *c*, secreting epithelium. Methylene blue; cochineal. Very highly magnified. (After von Smirnow.)

FIG. 416.—CAST OF THE PELVIS, INFUNDIBULA AND CALICES OF THE KIDNEYS OF A MAN.

Showing the expansion of the ureter, the subdivision of the pelvis, and the concave facets by which the calices fit over the apices of the renal pyramids (Hauch)

medulla, and at the border of the renal pyramid enters a renal column to unite with similar vessels coming from the borders of the adjacent pyramids. The union of these venous arcades forms large venous trunks which leave the renal columns, in company with the arteries, as the *venae propriae renales* (interlobar veins). They enter the connective tissue of the hilus, traverse the wall of the infundibula, major calices, and renal pelvis, and finally unite to form the *renal vein*.

The venulae rectae are peculiar in their typically straight course, and in the fact that the cells of their endothelium are extremely long. They frequently present a somewhat fibrous appearance, the elongated axis of the cell being parallel to the long axis of the vessel.

The capsule of the kidney is supplied by branches of the lumbar, phrenic, and suprarenal arteries, which form a rich, capillary plexus. These vessels anastomose with the terminal branches of the interlobular arteries of the kidney in the manner above described—a fact which acquires surgical importance from its relation to the establishment of a collateral circulation.

COURSE OF THE RENAL CIRCULATION

The above table may be useful as a résumé of the more important paths in the course of the renal circulation. In it the names of the several vessels are arranged in order and the arrows indicate the direction of the blood current.

Lymphatics.—The renal lymphatics consist of a superficial set which forms plexuses in the perirenal fat and deeper layers of the capsule, and a deep set which supplies the parenchyma of the organ. These two sets of lymphatic vessels are in communication by frequent anastomoses. The vessels of the superficial set convey their lymph to the neighboring lymph nodes of the lumbar region.

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COURSE OF THE RENAL CIRCULATION

Renal artery → Arteriae propriae renales → Arterial arcade → Interlobular arteries → Arteriolae rectae → Capillaries of the medulla; Afferent artery to renal corpuscle → Capillaries of the glomeruli → Efferent vessel from renal corpuscle → Capillaries of the cortical labyrinth → Venae stellatae → Interlobular veins → Venous arcade → Venae propriae renales → Renal vein. Venulae rectae → Venous arcade.

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tissue which here and there projects into the epithelial layer carrying with it the most superficial capillary vessels. The cells of the deeper layers divide by karyokinesis and push toward the surface to replace the more superficial cells which are gradually desquamated. Direct cell division occurs in the large plate-

FIG. 418.—TRANSITIONAL EPITHELIUM OF DOG'S URETER.

A, in the contracted condition; *B*, in the distended condition; *a*, basal layer of cubic cells; *b*, middle layer of polygonal cells; *c*, superficial layer of rectangular and ovoid cells. (Harvey.)

like cells of the superficial layer. The thin transitional epithelium of the calices is continuous with the columnar epithelium of the papillary ducts.

The *lamina propria*, continuous with the renal interstitial tissue, contains both collagenous fibers and elastic fibers. It is indistinctly divisible into a superficial denser portion, and an open-meshed deep portion whose fibrous bands loosely attach the mucous membrane to the muscular coat. This deep layer is analogous to the submucosa of the alimentary tract. The mucous membrane is thrown into numerous deep folds or rugae which in the ureter have a longitudinal direc-

RENAL PELVIS AND URETERS

The excretory passages of the kidney include the renal pelvis, the ureters, the urinary bladder and the urethra. All of these portions possess certain common characteristics. They have three coats, mucous, muscular, and fibrous, and are lined with a common type of epithelium, transitional, which extends from the renal pelvis to the prostatic portion of the urethra.

FIG. 417.—TRANSECTION OF URETER OF MAN.

E., transitional epithelium; *L. P.*, lamina propria; *C. M.*, circular muscle layer; *L. M.*, longitudinal muscle layer; *F.*, outer fibrous layer.

The *mucosa* of the renal pelvis and ureter is lined with transitional epithelium which rests upon a fibrous lamina propria. The epithelium consists of several cell layers, of which the superficial is formed by broad cuboidal cells, or thick flattened plates, whose form varies with the state of distention of the organ, and whose deep surfaces are indented by the rounded ends of the pear-shaped cells which form the deeper layers. The deepest cells are smaller and are irregularly spheroidal in shape. They are firmly attached to the underlying connective

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tion; this condition gives to the canal in transverse section a stellate appearance. Irregular folds or invaginations of the epithelium occur in the renal pelvis and have been described as glands, but true secreting glands are not found. Occasional lymphocytes occur in the mucosa, and small lymph nodules have also been found but cannot be regarded as of constant occurrence. The mucosa becomes

FIG 419—TRANSVERSE SECTION OF URINARY BLADDER OF DOG

a, b and c, compose the tunica mucosa, d, e and f, the tunica muscularis; g, tunica serosa, a, transitional epithelium, b, lamina propria mucosae; c, deep portion of tunica mucosa, corresponding to a tela submucosa, d, internal longitudinal muscle layer; e, middle circular muscle layer; f, external longitudinal muscle layer. The tunica mucosa is thrown into larger and smaller folds. ×20

gradually thinner as it is traced through the calices and infundibula and is reflected upon the surface of the renal pyramids.

The *muscular coat* of the ureter consists of a well-defined layer of circular fibers within which are many discrete bundles of longitudinal, smooth muscle. In the lower half of the ureter a third layer, whose fibers also have a longitudinal direction, is found outside the circular fibers. In this portion of the ureter, there-

fore, the muscular coat consists of three layers, an inner longitudinal, middle circular, and outer longitudinal.

In the renal pelvis and calices the muscular coat becomes progressively thinner toward the renal substance, and at the apex of the pyramid consists chiefly of circular fibers which are slightly thickened to form a sphincter about the papilla.
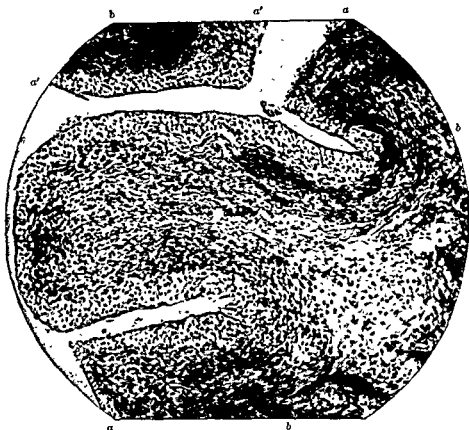
FIG 420.—THE MUCOSA OF A CHILD'S BLADDER IN THE CONTRACTED STATE OF THE ORGAN.

a-a, and a'-a', transitional epithelium; b, fibromuscular tissue of the mucosa. Hematein and eosin. Photo. ×216.

The outer fibrous coat of the ureter consists of areolar tissue which blends with that of the surrounding parts In the renal pelvis this coat becomes continuous with the connective tissue capsule of the kidney. (For development of excretory passages, see Chapter XV)

Blood Supply.—The larger blood vessels lie in the outer fibrous coat and distribute branches to the muscular coat and to the mucous membrane. In the latter they form a superficial capillary plexus which is in unusually intimate relation with the deeper cells of the lining epithelium.

Lymphatics.—The lymphatics begin in an intramuscular plexus and, by scanty vessels, in the deeper part of the mucosa They pass to larger vessels in the outer coat, which possess valves, and convey the lymph to the neighboring lymph nodes.

Nerves.—The nerves form a coarse plexus in the outer fibrous coat which contains many small ganglia. From this plexus motor fibers are distributed to the

muscular layers, and sensory fibers to the mucosa. The latter form a plexus
beneath the epithelium whence terminal fibers pass to end by minute end brushes in
the connective tissue and by varicose fibrils between the deep cells of the epithelium.

THE URINARY BLADDER

The wall of the urinary bladder closely resembles that of the ureter. It con-
sists of mucous, muscular and fibroserous coats. Its *mucous membrane* is lined
with transitional epithelium like that of the ureter and renal pelvis. It is there-
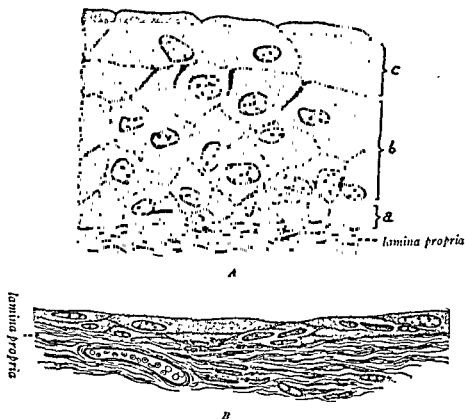
FIG. 421.—TRANSITIONAL EPITHELIUM OF DOG'S BLADDER.

A, in the contracted condition; *B*, in the distended condition. *a*, basal layer of cubic cells;
b, middle layer of polygonal cells; *c*, superficial layer of rectangular cells. (Harvey.)

fore impossible to determine from which of these portions detached epithelial
cells are derived when found by microscopical examination of the urine. Epithe-
lium may become detached from any portion of the excretory passages, and as
a result of inflammatory changes not only the superficial cells but also the deeper
pear-shaped cells may be desquamated.

The character of the epithelium varies with the collapse and distention of
the organ. When empty the mucous membrane is thrown into deep folds or
rugae, whose surface also presents secondary folds of irregular direction. The
epithelial layer is relatively thick, and is thicker on the sides of the folds than
upon either their apices or bases where the folding of the epithelium increases

the tension of its cells. When the organ is distended, the folds are more or less completely obliterated, the epithelial layer is much thinned, often until it appears to consist of no more than a double layer of cells, and its cells become much broader and relatively much thinner than in the collapsed or empty condition.[6] Hence the transitional variety of epithelium, with which the organ is lined, may be said to be remarkable for the extreme elasticity of its cells.

The mucous membrane, except near the urethral orifice, contains no glands. In this location, however, the bladder of adult man contains a few small mucus-secreting glands, lined with columnar cells. These are not present in infancy. They have been interpreted as vestigial prostatic tubules.

The lamina propria resembles that of the ureter and is loosely united to the underlying *muscular coat*.
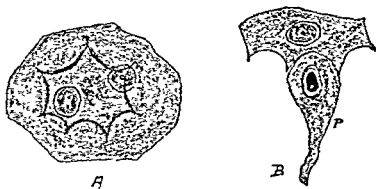
FIG. 422—EPITHELIAL CELLS FROM THE BLADDER OF THE RABBIT.

A, as seen from the under surface, showing the depressions made by the underlying polygonal and pyriform cells (*P*); *B*, side view of similar cell. (After Klein, from Schäfer.)

The *tunica muscularis* is formed by interlacing bundles of smooth muscle. It varies much in thickness according to the condition of the organ, being relatively thick when the viscus is empty and very thin when it is completely distended. In most portions three indistinct layers can be observed, a middle thick layer of circular fibers, and an inner and outer longitudinal layer. The outer longitudinal muscle is most distinct on the anterior and posterior surfaces of the organ.

The *tunica fibrosa* of the bladder consists of areolar tissue, having very broad meshes. In the lower portion of the bladder this coat blends with the connective tissue of the adjacent organs. Over the fundus of the organ it is clothed with peritoneal mesothelium

Vascular and Nerve Supply.—The vascular and nerve supply of the bladder is exactly similar to that of the ureter. The larger blood vessels occur in the outer fibrous coat, whence they distribute branches to the muscular coat and mucous membrane. Many small ganglia are also found in the outer coat, and motor and sensory nerves are distributed to the musculature and to the epithelium and connective tissue of the mucosa, as in the ureter.

[6] Harvey, R W., 1909

THE URETHRA

THE FEMALE URETHRA

. The mucosa of the female urethra is lined with a variable type of epithelium. Being continuous with the mucosa of the bladder, the epithelium of the urethra is at first of the transitional variety, but as it approaches the meatus this is changed to a stratified squamous type which is continuous with that of the vesti-
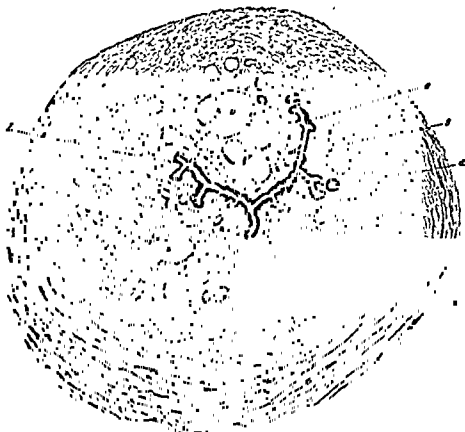
FIG. 423—TRANSECTION OF THE FEMALE URETHRA.

d, gland-like diverticulum; *e*, urethral epithelium; *L*, urethral lumen; *m*, striated fibers of the urethral muscle, *s*, erectile tissue of the lamina propria, containing many venous spaces and smooth muscle fibers. × 10 (Kolliker.)

bule. In certain individuals the superficial cells of the midportion of the urethra are much elongated. In such cases they assume an irregular stratified columnar form.

The epithelium rests upon a lamina propria of dense areolar connective tissue whose outer portion blends with a looser connective tissue which contains many broad venous channels and forms a sort of spongy erectile tissue. This erectile coat is surrounded by a thin muscular coat whose innermost fibers, longitudinal in direction, are continued outward to the meatus, and whose outer circular fibers,

deficient toward the meatus, are often slightly thickened near the neck of the bladder to form an indistinct sphincter urethrae muscle. This coat contains occasional striated muscle fibers. The female urethra is scantily supplied with *urethral glands* which open near the meatus and supply a meager mucoid secretion.

THE MALE URETHRA

The male urethra conducts the urine from the bladder to the surface, its course being through the axis of the corpus spongiosum of the penis (Fig. 454). It forms the terminal segment also of the genital canal and conducts the semen. It accordingly performs a double function, serving both the urinary and the male reproductive system. The character of its epithelium is variable, not only in its successive portions, but it is also subject to great individual variation. Like that of the bladder and ureter it changes its appearance according as the canal is collapsed or distended. In the first or prostatic portion of the urethra the epithelium is of the transitional type; in the membranous and penile portion its superficial cells are elongated so that the epithelium usually acquires a stratified columnar form; near the meatus the type is again exchanged for a stratified squamous epithelium which is continuous with that of the glans penis.

The lamina propria of the urethra consists of areolar tissue in which are embedded the small branched tubulo-acinose *urethral glands* (of Littré) lined with columnar, mucus-secreting cells. These glands are more abundant along the upper surface. The mucosa also contains frequent lacunar invaginations of the epithelium, and is thrown into longitudinal rugae, its lumen being obliterated except when distended by the passage of urine.

The lamina propria, and especially that portion which is distant from the urethral canal, is permeated by the thin-walled broad venous spaces of the erectile tissue of the corpus spongiosum (*corpus cavernosum urethrae*). The septa between these venous spaces, in addition to the dense areolar tissue of which they chiefly consist, contain many bundles of longitudinal smooth muscle. In the deeper portions of the urethra circular muscle fibers are also found in the outer part of this coat, and near the orifice of the bladder they are somewhat thickened to form the sphincter urethrae. Moreover, the corpus spongiosum is invested with a thick sheath of dense fibrous connective tissue. At the apex of the prostate circularly disposed striped muscle fibers form a second urethral sphincter, the external vesical sphincter.

Nerve Supply.—The nerve supply of the urethra includes both sensory and motor spinal fibers, and sympathetic fibers for the smooth muscle and the blood vessels.

CHAPTER XV

THE REPRODUCTIVE SYSTEM

The reproductive system differs widely in the two sexes. The several organs involved are, however, in general strictly homologous in male and female. The differences result from a divergent specialization related to a division of function in the reproductive act and process. The specialization involves both progressive and regressive changes, the latter producing certain vestigial appendages, of dif-

Sinus prostaticus

Urinary Bladder

Ampulla of ductus deferens

Seminal vesicle

Corp. cav urethrae

Paradidymis

Ductuli efferentes

Ductulus abberans

Ductus epididymidis

Prepuce

Glans penis

Fossa navicularis

Rete testis

Tubuli recti

Appendix testis

Tubuli contorti

Appendix epididymis
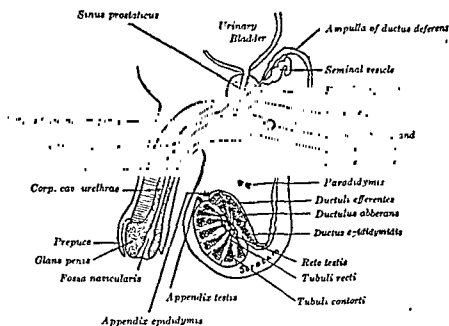
FIG. 424.—MALE GENITALIA. (Adapted from Merkel.)

Oviduct

Paroöphoron

Isthmus

Epoöphoron

Ampulla

Uterus

Fimbriae

Ostium abdominale

Broad ligament

Ovary

Hydatid of Morgagni

Ovarian ligament

Fimbria ovarica

Vagina
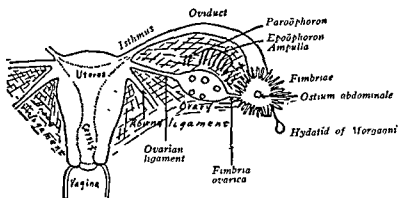
FIG. 425.—FEMALE INTERNAL GENITALIA

ferent origin in the two sexes. The male organs of reproduction include a primarily and essentially internal group of genital organs, namely a pair of testes and their associated ducts, glands and appendages; and an external genital organ, the penis (Fig. 424). The female organs of reproduction likewise include an internal group of genitalia, namely a pair of ovaries with their ducts and the associated glands and appendages; and a group of external genitalia and glands (Fig. 425). The essential sex organs are the testes and ovaries, respectively.

DEVELOPMENT

The original primordia are the same in both sexes. They include essentially: a pair of undifferentiated *sex glands or gonads* located on the mid-ventromesial side of each fetal kidney (wolffian body or mesonephros); a double pair of par-
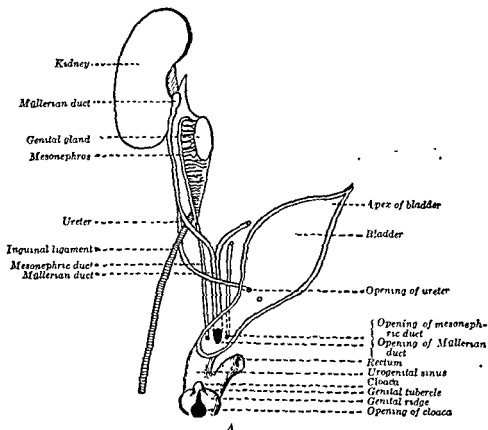
FIG. 426—THE METAMORPHOSES OF THE INDIFFERENT (*A*) UROGENITAL SYSTEM INTO THE
MALE (*B*), AND FEMALE (*C*) SYSTEMS. (From Polak, after Hertwig.)
(See p. 428 for *B* and *C*.)

allel canals, the fetal wolffian (mesonephric) ducts and the müllerian ducts. An embryo at this stage of development (13 millimeters, Fig. 223, about 45 days) is said to be in the indifferent sexual stage. The ducts communicate terminally with the gonads and with the exterior. Subsequently they undergo a different development, as do also the terminal associates (gonads, and urogenital sinus, respec-

Diagram B labels (top figure):

Kidney

Appendage of testicle
(Hydatid of Morgagni)

Epididymis
Testis
Paradidymis
Deferent duct

Müllerian duct
Gubernaculum testis
Ureter
Seminal vesicle
Deferent duct

Epididymis
Testis
Gubernaculum testis

Apex of bladder
Bladder
Opening of ureter
Urethra
Opening of ejaculatory duct
Prostate

Urethra   Sinus prostaticus

B

Diagram C labels (bottom figure):

Kidney

Hydatid

Oviduct (fimbria)
Epoöphoron
Ovary
Paroöphoron
Mesonephric duct

Oviduct
Epoöphoron
Ovary
Ovarian ligament
Uterus
Round ligament
Vagina

Apex of bladder
Bladder
Ureter
Urethra
Vestibulum vaginae

C

FIG. 426 B, C.

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FIG. 427.—THE PROCESS OF MATURATION IN THE MALE (*A*) AND FEMALE (*B*) GAMETES.
(Boveri.)

tively) in the two sexes. For the details of this process reference must be made to textbooks of embryology. The primitive gonads in the female develop into the ovaries, in the male into the testes. In the female the müllerian ducts become the oviducts, and fuse proximally to form the uterus and vagina; in the male, these ducts suffer regressive changes and persist only as vestiges: an appendix for each testis, and the unpaired sinus pocularis. On the contrary, the wolffian duct becomes vestigial in the female, persisting as the appendix fimbriae (hydatid of Morgagni) and the canal of Gartner; while in the male it develops into the main portion of the definitive duct system: ductus epididymidis, and ductus deferens. The tubules of the fetal kidney (wolffian body) also contribute to the excretory duct system.

ADULT MALE AND FEMALE DERIVATIVES OF THE FETAL (INDIFFERENT)
REPRODUCTIVE SYSTEM *

INTERNAL GENITALS		
Indifferent Stage	Male	Female
Genital ridge	Testis Gubernaculum (in part) Mesorchium	Fimbria ovarica Ovary Ovarian ligament Mesovarium
Wolffian body (tubules) (mesonephros)	Globus major of epididymis (ductuli efferentes) *Paradidymis* *Ductuli aberrantes* *Appendix of epididymis* *(stalked hydatid)*	*Epoöphoron (parovarium, organ of Rosenmüller)* *Paroöphoron*
Wolffian duct (mesonephric duct)	Duct and globus minor of epididymis Ductus deferens Seminal vesicle Ejaculatory duct	*Chief vesicular appendage (hydatid of Morgagni)* *Collecting tubule of epoöphoron* *Canal of Gartner*
Müllerian duct	*Appendix testis (sessile hydatid)* *Sinus pocularis (uterus or vagina masculina, or utriculus prostaticus)*	Oviducts (uterine or fallopian tubes) Uterus Vagina
EXTERNAL GENITALS		
Urogenital sinus	{ Prostatic and membranous } { portions of male urethra }	Urethra Vestibule
Genital tubercle	Penis	Clitoris
Genital folds		Labia minora
Genital swellings	Scrotum	Labia majora

* The vestigial structures are given in italics, synonyms in parentheses.

In the male, a cephalic group of from 10 to 15 tubules persists to form the ductuli efferentes; a caudal group becomes vestigial forming the ductuli aberrantes, the paradidymis and the appendix epididymidis. In the female, these ducts early disappear for the most part—a variable number persisting as vestigial structures: the epoöphoron and the paroöphoron.

The seminiferous tubules of the testis, including the tubuli recti and the rete testis, arise as solid cords of cells. These cords subsequently acquire a lumen, and connect with the efferent tubules. In the ovary likewise such cell cords (sex cords) appear, continuous with the peritoneal (germinal) epithelium; from these in part develop the ovarian follicles with their ova.

The outline on the preceding page summarizes in tabular form the main facts regarding the development of the reproductive system.

In both sexes the wolffian duct proximally sprouts a duct which dilates and subdivides distally, meanwhile separating from the parent duct and making a secondary connection with the developing bladder. The subdivisions elongate to form the collecting portions of uriniferous tubules, and unite with ontogenetically distinct tubules (the secretory portions or nephrons) to form the complete renal tubules. The original dilatation and earlier subdivisions become the pelvis and calices respectively, and the proximal portion of the original primordia persists as the ureter.

GAMETOGENESIS

The study of the sex or genital glands, the *ovary* and the *testis*, is perhaps best approached by way of a consideration of the mechanism by which they perform their respective specific functions, namely the production of *ova* and *spermatozoa* ripe for union. The common process is known as *gametogenesis*. The end products are the male and female *gametes*, or spermia and ova. In the male the process is known as *spermatogenesis*, in the female, *oogenesis*. The act of subsequent union of the gametes is called *fertilization*, and the fertilized egg is the *zygote*.

The result of gametogenesis is the preparation of a primary germ cell for union with a gamete from the opposite sex. The essence of the process is known as *maturation* (meiosis), and involves prominently mitotic cell division. However, the method of division is not of the simple homeotypic type, where a chromosome simply divides *longitudinally* into two daughter chromosomes, but it is of the type called *heterotypic*, the chief characteristic of which is the formation of *tetrads*. The latter are of various sorts, all, however, characterized by a four-lobed condition representing a quadripartite *double* or *bivalent* chromosome (Fig. 428).

Both sperms and eggs trace their ancestry back to primordial germ cells, indistinguishable in the sexually undifferentiated organism, except for a *difference in chromosome content*, which difference is commonly indiscernible. In certain instances, *e.g., Ascaris*, the germ cell can be distinguished from the soma cell at the two-cell stage. In a number of vertebrates, *e.g.*, dogfish, turtle, etc. (Allen), the *primordial germ cell has been traced from a position among the entoderm cells lining the gut of the young embryo through a migration into the differentiating *gonad*, ovary or testis. Swift[1] has traced the primordial germ cells in the chick from a crescentic area in the entoderm in front of the head end of the primitive streak, through their migration to the gonad by way of

[1] Swift, 1914.

FIG. 428—SUCCESSIVE STAGES IN HUMAN SPERMATOGENESIS.

From Evans and Swezy, *The Chromosomes in Man, Sex and Somatic,* Memoirs of the University of California, 1929, 9 1.

1 Spermatogonial plate with 48 chromosomes, including a small y-chromosome.

the developing blood vessels. The earlier anatomists, on the other hand, derived the primordial germ cells from the mesothelial covering (germinal epithelium) of the germ gland region of the primitive kidneys, the mesonephroi. This mode of origin, either exclusively or in part, is still supported by certain investigators.

Whatever the actual source of origin—whether entodermal or mesodermal, whether specific or general—and whenever the time of differentiation, whether early or relatively late, the primordial germ cells in the gonad undergo extensive proliferation, increasing greatly in numbers. The earlier generations may be inclusively designated primary spermatogonia and oogonia respectively, the final generation taking the term secondary gonia. The question of the origin of the primordial germ cells bears upon the hypothesis of the continuity of germ plasm.

Spermatogenesis.—Since gamete formation is easier to follow in the male, though apparently a more highly specialized process, it seems of advantage first to describe spermatogenesis. The description may begin with the last generation of *spermatogonia*, the so-called secondary spermatogonia. These cells contain 48 chromosomes, the *diploid* number (Fig. 428, 1). The chromosome complex includes a pair of sex chromosomes (heterochromosomes; allosomes). This pair consists of a larger x-chromosome and a smaller y-chromosome. The other 46 chromosomes are designated euchromosomes or autosomes. During the resting stage following the final spermatogonial *mitosis*, the daughter cells, now known as *primary spermatocytes*, undergo a slight amount of growth (2-4). The nucleus stains only slightly; the chromatin becomes arranged in the form of a delicate spirem (leptonema, 4); the nucleolus is conspicuous as a relatively large, deeply staining spheroidal body. The unequal heterochromosomes have fused into a single, conspicuous, generally bilobed, bivalent sex chromosomes (accessory chromosome). The primary spermatocyte during these early growth stages is designated the auxocyte.

The leptotene spirem stage (4) is followed by a double spirem (diplotene) condition

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2. Primary spermatocyte at beginning of maturation process. The resting nucleus of the interkinetic stage following the last spermatogonial division is in the protobroch phase. *SC*, sex chromosome (heterochromosome). The lighter spheroidal body is the nucleolus.

3 Deutobroch nucleus of primary spermatocyte. The chromatin network is in process of transformation into the leptotene spirem.

4 Leptonema, with complete spirem.

5 Synaptonema. The filamentous chromosomes are arranged in 24 pairs.

6 Later stage of synapsis. Both heterochromosome and nucleolus are conspicuous.

7 Late stage in transition from synapsis to synizesis.

8 Synizesis stage of primary spermatocyte.

9 Pachynema, at the beginning of the unraveling of the chromosomes from synizesis.

10 Diffuse stage of first maturation division.

11 Later diffuse stage. Heterochromosome near center, its unequal components (X and Y) joined with slender thread.

12. Late diakinesis, showing 24 pairs of compact chromosomes (tetrads) including the sex chromosome (X-Y).

13 Early prophase of the first maturation d—————

14. Later prophase of ——

15 Late prophase of f

16. Beginning of metaphase of dividing primary spermatocyte.

17 Primary spermatocyte at early metaphase; the spindle holds 24 tetrad (bivalent) chromosomes.

18. Primary spermatocyte, the metaphase spindle holds 24 tetrads.

19. Primary spermatocyte at anaphase.

20 Secondary spermatocyte at late prophase. The spindle holds 24 univalent chromosomes (dyads).

during which transverse segmentation occurs, resulting in the reduction of the number of chromosomes from 48 to 24, the *haploid* number. The segmentation products consist of 24 paired or bivalent chromosomes. This condition of the nucleus is designated the synaptonema. The members of each pair of chromosomes are assumed to be homologous and to represent a contribution from the male and female parent, respectively. The side by side union of the chromosomes during synapsis is called parasynapsis. In some lower forms the synaptic union is end-to-end, designated telosynapsis. During later phases of synapsis the chromosomes become more compact and stain more intensely (6); they become looped, their ends attaching themselves to the nuclear membrane in the region
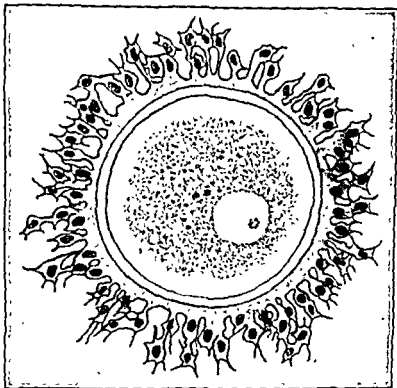
Fig 429—Full Grown Human Primary Oocyte.

Fresh specimen examined in liquor folliculi Nucleolus, nucleus, vitellus, egg-membrane, perivitelline space and enveloping corona radiata appear in the order named from center to periphery. (*Waldeyer.*)

of the idiosome (7). The final stage of this process of polarization, during which the polar mass of looped bivalent chromosomes contracts, is known as synizesis (8). Subsequently, during postsynapsis the chromosomes unravel, and pass first through a so-called pachytene stage when the chromosomes stain deeply (9), and then through a diffuse stage (10, 11), into the prophase stages with typical tetrads (12-16). Meanwhile the x-y pair of chromosomes has remained conspicuous. These primary spermatocytes pass through typical mitotic stages (16-19), the tetrads dividing into dyads, and the bivalent heterochromosome separating into its x and y sex chromosomes. The resulting daughter cells, the *secondary spermatocytes*, contain each 23 dyads, half with an additional x-chromosome, the other half with an additional y-chromosome.

The ensuing division of these secondary spermatocytes produces *spermatids* (Fig.

435 C) each with 24 chromosomes, one half of the spermatids with an x-chromosome, the other half with a y-chromosome. The spermatids metamorphose into *sperms*. The sperms differ with respect to the sex chromosome. Those that contain the x element are female determining; those with the y element are male determining. At fertilization zygotes are produced with 48 chromosomes; but these differ in that some have an x-y pair of chromosomes, some an x-x pair. The former develop into males, the latter into females. The process of chromosome reduction involved in the maturation mitoses is known as *meiosis*. The interval between the *reductional* or first maturation mitosis and the *equational* or second maturation mitosis is the *interkinesis*.
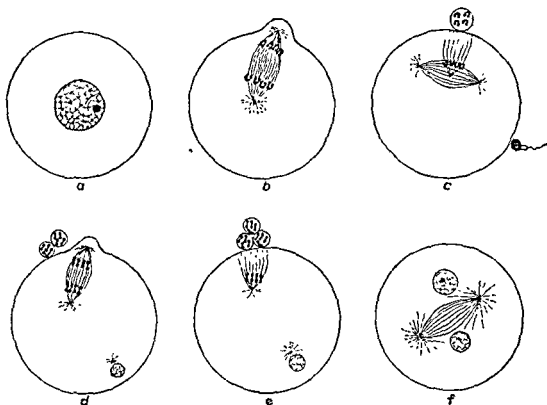
FIG. 430—THE MATURATION OF AN OVUM.

a, fully-grown secondary oogonium or ripe ovum, a primary oocyte in postsynaptic resting condition; *b*, first maturation spindle at anaphase; *c*, first polar body formed, second maturation spindle organizing, sperm entering, the egg now a secondary oocyte; *d*, second maturation spindle at anaphase, first polar body divided, male pronucleus formed from sperm head, *e*, second polar body formed, egg now an ootid or mature ovum, the chromosomes remaining in the egg are beginning to fuse into a pronucleus, *f*, female pronucleus complete, the first cleavage spindle organizing between the two pronuclei Each pronucleus will contribute 24 chromosomes, the female group always including an X chromosome, the male group either an X or a Y chromosome. The zygote, accordingly, contains 48 chromosomes, including either an XX (female) or an XY (male) pair of sex chromosomes.

Oogenesis.—In contrast to the spermatozoon, which is relatively minute, highly motile, and carries a minimum amount of cytoplasm, the egg on the other hand grows enormously in size. In the starfish, for example, the ratio of sperm to egg is approximately 1:500,000. The egg is non-motile, and has a large amount of cytoplasm heavily laden with yolk material. This phase of the oogenesis is known as the growth period. During the early portions of this period synapsis occurs, and subsequently chromatic material

(chromidia) appears in the cytoplasm, presumably extruded by the nucleus, and in part at least changed into yolk. This generation is the *primary oocyte* (Fig. 429), the preceding generation being oogonial, primary and secondary, characterized by extensive proliferation. The primary oocyte divides in a manner similar to the primary spermatocyte, that is by heterotypic mitosis, but the daughter cells are very unequal in size, each, however, with the same number of chromosomes (24). The small abortive cell is called the *polar body*, or better *polocyte*, while the large cell becomes a *secondary oocyte*. Both polocyte and secondary oocyte again divide, the end-result being three similar polar bodies and one large *oötid* or *mature ovum*, now ready for fertilization.

FIG. 431.—THE TESTICLE WITH ITS SYSTEMS OF EFFERENT PASSAGES.

Natural size. (Toldt.)

It must be recalled that the maturation process is in essence a process of eliminating one-half of the original quota of chromosomes, and a quantitative reduction of its original amount of chromatin to one-fourth. All of the mature eggs contain an x-chromosome. At fertilization, by fusion of egg and sperm, the specific number of chromosomes is reëstablished—differing in many cases in male and female of the same species—and the chromosomes by growth regain or even exceed their original size. With this brief consideration of the function of the germ glands in general, we may proceed to a description of the structure of the male organs of reproduction and subsequently of the female organs.

MALE ORGANS OF REPRODUCTION

These organs include the penis and the testes, together with their accessory glands, and the excretory ducts which connect the testes with the urethral canal. The excretory ducts include the epididymis, ductus (vas) deferens, seminal vesicles,

and ejaculatory ducts; and with their termination in the urethra there are connected the ducts of the prostate gland and the bulbo-urethral glands (of Cowper), whose secretion mixes with that of the testes to form the semen. The male urethra serves the double function of a *urogenital canal.*

INTERNAL GENITAL ORGANS

Testis

The testis is to be regarded as a gland with a double function; it produces cells (spermatozoa), hence *cytogenic gland;* and an internal secretion, hence, in part an endocrine gland. In connection with the testis must be considered also its excretory duct system, and the various glands accessory to it. The relationship of these various structures is shown in Figure 424.
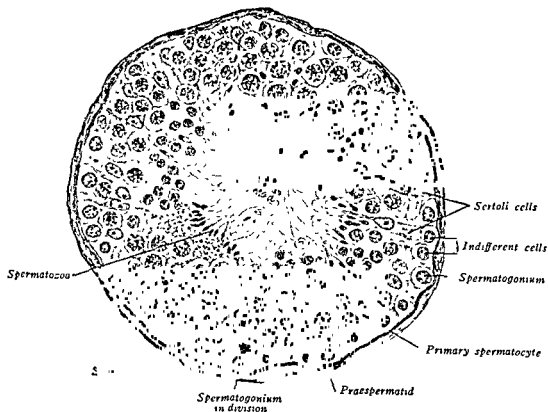
FIG. 432—TRANSVERSE SECTION OF A SEMINIFEROUS TUBULE OF A NINETEEN-YEAR-OLD MAN. ×550. (Braus)

The testis is encased in a robust fibro-elastic capsule, the *tunica albuginea,* the innermost layer of which is of looser texture and very vascular, hence called the *lamina vasculosa* External to the albuginea is a double-layered sac of peritoneum, the *tunica vaginalis,* its visceral layer closely adherent to the capsule. The human

(chromidia) appears in the cytoplasm, presumably extruded by the nucleus, and in part at least changed into yolk. This generation is the *primary oocyte* (Fig. 429), the preceding generation being oogonial, primary and secondary, characterized by extensive proliferation. The primary oocyte divides in a manner similar to the primary spermatocyte, that is by heterotypic mitosis, but the daughter cells are very unequal in size, each, however, with the same number of chromosomes (24). The small abortive cell is called the *polar body*, or better *polocyte*, while the large cell becomes a *secondary oocyte*. Both polocyte and secondary oocyte again divide, the end-result being three similar polar bodies and one large *oölid* or *mature ovum*, now ready for fertilization.

Ductus deferens

Ductus epididymidis

Lobuli epididymidis

Ductulus aberrans superior

Corpus epididymidis

Ductulus aberrans (inferior)

FIG. 431.—THE TESTICLE WITH ITS SYSTEMS OF EFFERENT PASSAGES.

Natural size. (Toldt.)

It must be recalled that the maturation process is in essence a process of eliminating one-half of the original quota of chromosomes, and a quantitative reduction of its original amount of chromatin to one-fourth. All of the mature eggs contain an x-chromosome. At fertilization, by fusion of egg and sperm, the specific number of chromosomes is reëstablished—differing in many cases in male and female of the same species—and the chromosomes by growth regain or even exceed their original size. With this brief consideration of the function of the germ glands in general, we may proceed to a description of the structure of the male organs of reproduction and subsequently of the female organs.

MALE ORGANS OF REPRODUCTION

These organs include the penis and the testes, together with their accessory glands, and the excretory ducts which connect the testes with the urethral canal. The excretory ducts include the epididymis, ductus (vas) deferens, seminal vesicles,

The walls of the seminiferous tubules consist of fibro-elastic tissue. They are lined with a several-layered epithelium, the cells representing the several stages of spermatogenesis. In addition to the germ or sex cells, the epithelium contains sustentacular cells (Sertoli cells), to which the spermatids become attached during process of metamorphosis into ripe spermatozoa (spermia). It seems probable that the spermatids also draw nourishment from the sustentacular cells for the work of metamorphosis, hence they are also known as "trophocytes." The sustentacular cell is roughly of tall columnar shape, tapering somewhat irregularly toward the
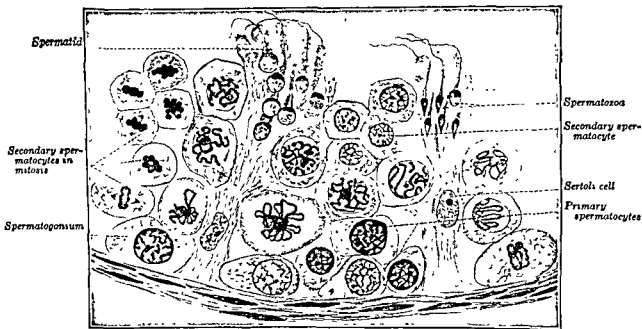
FIG. 434.—PORTION OF A TRANSECTION OF A SEMINIFEROUS TUBULE FROM THE HUMAN TESTIS, ILLUSTRATING THE VARIOUS STAGES IN SPERMATOGENESIS.
(From Polak, after Retzius.)

distal pole. The proximal pole contains the nucleus and frequently flares somewhat giving the entire cell a tall pyramidal shape. The nucleus is pale and contains one or several chromatic nucleoli. The spermatozoa are embedded head first, four to eight or more to a cell, in the protoplasm of the trophocyte. Such a composite group constitutes a so-called *spermatoblast* of von Ebner. The sustentacular cell contains one or several crystalloids Their origin and function is unknown. They were regarded by Montgomery as probably sustentacular cell determinants, having been traced by him from the common mother cells of both trophocyte and spermatogonium into the former, the latter being said to lack these elements. However, Winiwarter (Fig. 433) reports similar crystalloids in both trophocytes and spermatogonia In the undescended testes of cryptorchids the degenerate seminal tubules are lined with only one type of epithelium, the constituent cells representing probably the common ancestor of trophocytes and sperm cells.

testis measures about one and one-half inches in length, one inch in width and three-fourths inch in thickness. Septa continuous with the capsule divide it into a number of compartments or lobules, pyramidal in shape, the apices converging to an anterodorsal mass of dense connective tissue, the *mediastinum testis (corpus highmorianum)*, corresponding to a hilus. The lobules contain each several,
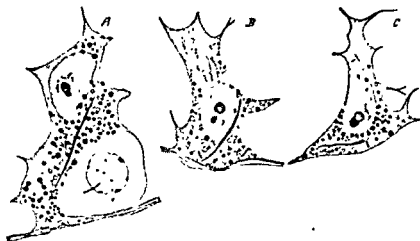
FIG 433—SERTOLI CELLS OF THE HUMAN TESTIS.

A, showing a crystalloid (of Charcot) . . . . to the right a spermatogonium with a crystalloid (of . . . . accessory rods, and lipoid granules and droplets. *C* . . . . ssory rod, and at the summit two accessory rods ×600. (Winiwarter.)

frequently two, extensively convoluted tubules, the seminiferous tubules (tubuli contorti). When uncoiled they measure from one to two feet. The entire testis contains several hundred lobules; the number has been variously estimated at from one hundred to four hundred.

Bremer[2] describes the tubuli contorti of man as tubules that may be single, ending blindly, may branch or may anastomose. Huber and Curtis,[3] on the contrary, state that in the adult rabbit the seminiferous tubules "present no blind ends, diverticular or nodular enlargements." Their simplest form is that of an arch beginning and ending in a tubulus rectus. The two limbs may lie in adjacent lobules. Complex tubules are also described, resulting from the linkage of from three to twelve simple arched tubules. According to Curtis[4] branches and anastomoses of seminiferous tubules are infrequent in the mouse testis, more frequent in dog, and most frequent in rabbit.

The testis is lodged in the *scrotum*. The wall of the scrotum is essentially like the general integument, except that it may be more highly pigmented. Its subcutaneous layer, however, is looser in texture and contains more elastic tissue and smooth muscle. It is known as the *dartos*. It has a thermoregulatory function related to spermatogenesis[5]

[2] Bremer, 1911.
[3] Huber and Curtis, 1913
[4] *Curtis,* 1915.
[5] Moore 1924

Every section of a tubule of an active testis contains several, sometimes all the stages of spermatogenesis. Since the spermatogenetic process generally travels in waves, a longitudinal section is most favorable for a study of the continuous process.

From wall to lumen of the tubules there can be seen, at successive levels, spermatogonia, primary spermatocytes, secondary spermatocytes (prespermatids), spermatids, and spermatozoa attached to the tips of the sustentacular cells. Mitoses can frequently be seen in spermatogonia, primary and secondary spermatocytes. The primary spermatocytes are the largest of the germ cells; the secondary spermatocytes are approximately half the size and lie distal, while the spermatids are approximately one-fourth the size; the spermatids may be at any stage of a continuous process of metamorphosis involving nuclear, cytoplasmic, and general form changes. The spermatogonia are of various sizes, frequently approximating that of the primary spermatocytes, but always lie peripherally, on the basement membrane between sustentacular cells. The above named marks constitute the grosser criteria for identifying the several generations of cells involved in spermatogenesis.

Spermatozoon.—The sperms, or spermatozoa, represent metamorphosed spermatids (Fig. 435). The spermatid nucleus becomes progressively more compact, chromatic and smaller. At the same time it moves toward one pole of the cell, the cytoplasm flowing backward, except for a thin envelope (galea capitis) which terminally forms a covering for the *perforatorium* which represents a portion (acrosome) of the original idiosome. The idiosome is the germ-cell representative of the archoplasmic complex. It is enveloped by the Golgi apparatus. Concurrently with the changes outlined for the nucleus the idiosome liberates a centrosome, and centrosome and acrosome pass to opposite poles of the nucleus. The centrosome divides into two moieties, a proximal, which becomes attached to the nuclear membrane, and a distal, which moves peripherally at the same time sprouting a flagellum, the *central filament*. Meanwhile a peripheral portion separates from the more central portion of the distal centrosome and moves backward over the central filament inclosing an enveloping column of cytoplasm, the *middle piece*, in which mitochondria have aggregated. In many mammals, possibly in man, the mitochondria fuse to form a filament, the *spiral filament*, which becomes spirally arranged about the central filament. However, Gatenby and Beams,[6] in their description of spermogenesis in man note "the apparent absence of any form of spiral body in the middle-piece." The central filament continues to grow distally

in the formation of a mature sperm; K, mature sperm (after Retzius) as seen en face. a, acrosome; ch, chromosomes, c, centrioles; dc, distal centriole, dc^1, granular derivative, and dc^2, ring derivative, of the distal centriole; e, "manchette," head sheath; f, tail or axial filament; g, Golgi apparatus plus idiosome (idiosomic substance represented by stipple); h, sperm head (nucleus plus acrosome); k, neck region, m, mitochondria; ms, mitochondrial spiral; n, nucleus; pc, proximal centriole; r, protoplasmic remnant; s, sheath of the tail filament; t^1, middle piece, t^2, principal piece, and t^3, end piece of tail. (From Arey, *Anat. Rec.*, 1930, 47.)

[6] Gatenby and Beams, 1935

FIG 435.—SUCCESSIVE SEMIDIAGRAMMATIC STAGES IN THE DEVELOPMENT OF THE HUMAN
SPERMATOZOON. ×1760.

A, primary spermatocyte, protobroch stage; *B*, metaphase of primary spermatocyte division;
C, spermatid immediately after the secondary spermatocyte division; *D* to *H*, earlier stages in
the transformation of the spermatid into a sperm; *I* (en face) and *J* (profile view), late stages

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Every section of a tubule of an active testis contains several, sometimes all the stages of spermatogenesis. Since the spermatogenetic process generally travels in waves, a longitudinal section is most favorable for a study of the continuous process.

From wall to lumen of the tubules there can be seen, at successive levels, spermatogonia, primary spermatocytes, secondary spermatocytes (prespermatids), spermatids, and spermatozoa attached to the tips of the sustentacular cells. Mitoses can frequently be seen in spermatogonia, primary and secondary spermatocytes. The primary spermatocytes are the largest of the germ cells; the secondary spermatocytes are approximately half the size and lie distal, while the spermatids are approximately one-fourth the size; the spermatids may be at any stage of a continuous process of metamorphosis involving nuclear, cytoplasmic, and general form changes. The spermatogonia are of various sizes, frequently approximating that of the primary spermatocytes, but always lie peripherally, on the basement membrane between sustentacular cells. The above named marks constitute the grosser criteria for identifying the several generations of cells involved in spermatogenesis.

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in the formation of a mature sperm; *K*, mature sperm (after Retzius) as seen en face *a*, acrosome, *ch*, chromosomes; *c*, centrioles; *dc*, distal centriole; *dc*¹, granular derivative, and *dc*², ring derivative, of the distal centriole; *e*, "manchette," head sheath; *f*, tail or axial filament; *g*, Golgi apparatus plus idiosome (idiosomic substance represented by stipple); *h*, sperm head (nucleus plus acrosome); *k*, neck region; *m*, mitochondria, *ms*, mitochondrial spiral; *n*, nucleus; *pc*, proximal centriole, *r*, protoplasmic remnant, *s*, sheath of the tail filament; *t*¹, middle piece, *t*², principal piece, and *t*³, end piece of tail. (From Arey, *Anat. Rec.*, 1930, 47.)

[6] Gatenby and Beams, 1935.

beyond the final locus of the ring centrosome, and together with an envelope of cytoplasm constitutes the tail of the spermatozoon. A short terminal naked portion of the central filament is known as the *terminal filament*. During the later stages of metamorphosis (Fig. 435, *G-II*) a distal portion of the cytoplasm separates from the spermatid and eliminates the Golgi apparatus and some of the mitochondria.

Summarizing the above: The nucleus becomes the head of the spermatozoon. This is tipped with an acrosome, a derivative of the idiosome, and covered by the galea capitis, the two comprising the perfora-
torium. The other constituents of the idiosome contribute the central filament. The extent between distal and proximal centrosomes constitutes the *neck*; the portion between distal centrosome and ring centrosome the *connect-ing* or *middle piece* (body), with its spiral filament derived from mitochondria. The tail or flagellum consists of central filament enveloped by cytoplasm. In many forms a *spiral fin* develops on the tail. Also, there is endless variation with reference to the shape of the head. But the development and morphology of spermatozoa of all vertebrate forms is essentially the same. At fertilization only head and middle piece—nucleus and centrosome and mitochondria—enter into the egg, the tail being generally left behind.

The *human spermatozoon* has a length of from fifty to sixty microns. Of the total the head constitutes about 5 μ, the middle piece about 5 μ and the end-piece about 10 μ. Seen *en face* the head has an ovoid shape; in profile it appears pyriform, due to a thinning along its terminal margin. Occasionally atypical or monstrous, double-headed, multiple-tailed, and giant spermatozoa appear; but these are probably nonfunctional. Though flagellate, the

FIG. 436—HUMAN SPERMATOZOON.
(After Bonnet)

spermatozoa are non-motile until they reach the epididymis, where they become bathed in a secretion. Their motility, however, is not pronounced until they reach the place in the excretory passage where the secretion of the seminal vesicles, prostate and bulbo-urethral glands are present. The mixture of these secretions with the sperm forms the *semen*.

The spermatozoa can withstand considerable variations in temperature, but they are very susceptible to acid solutions; they survive best in slightly alkaline media. Under favorable conditions spermatozoa may be kept alive for as long as

eight days. It is probable that they remain alive for even a longer time in the female genital tract; but it is uncertain whether they can maintain their functional virility for this length of time. The number of spermatozoa per cubic millimeter has been estimated at 60,876; and the total in an average ejaculation at 200,000,000 (Lode, 1896).

FIG. 437.
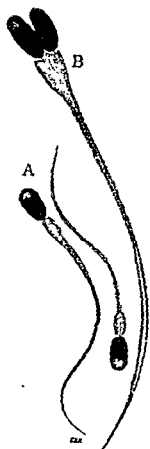
FIG. 438.

FIG. 437.—SPERMATOZOA OF VARIOUS ANIMALS.

A, from the badger; *B*, from the bat. Redrawn after Ballowitz. ×1200 *C*, from the rat. Hematein and eosin ×1200

FIG. 438.—SPERMATOZOA FROM THE SEMEN OF MAN.

A, usual type; *B*, "giant" double spermatozoon. Hematein and eosin ×1200.

The *tubuli contorti* pass into short *tubuli recti* and the latter into the rete testis of the mediastinum. The rete testis is the beginning of the excretory duct, and consists of a meshwork of irregular tubules lined with a single layered cuboid cuboid nonciliated epithelium. They connect with a group of greatly coiled tubules, the ductuli efferentes, from ten to fifteen in number, each terminally winding so as to assume a conical shape, hence *coni vasculosi*—which tubules empty into the distal portion of a common duct—the *ductus epididymidis*. This portion of the

duct, together with the efferent ductuli, constitute the *globus major* of the epididymis (*caput epididymidis*). Consideration of the duct system will follow below.

Interstitial Cells of Leydig.—Here should be considered the intertubular connective tissue of the testis. Fibro-elastic connective tissue acts as a supporting stroma for the testicular parenchyma of the seminiferous tubules. Throughout this stroma, between the adjacent tubules, occur peculiar large polygonal cells, the *interstitial cells* of Leydig, either scattered or arranged in masses. The condi-
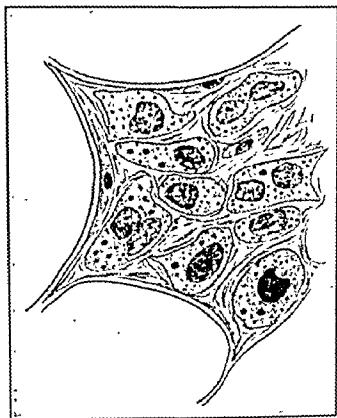
FIG. 439.—A GROUP OF INTERSTITIAL CELLS FROM THE TESTIS OF A THIRTY-FIVE-YEAR-OLD NEGRO.

The outlines of three adjacent seminiferous tubules are shown. Among the interstitial cells are three nuclei of ordinary connective tissue. The interstitial cells are filled with lipoid spherules and granules. Formalin fixation, iron hematoxylin stain. × 1500.

tion of the nucleus varies from pale vesicular to dense deeply chromatic. Division figures are exceedingly rare among them, though an occasional cell may, in young testes, be seen in mitosis. In older testes an occasional nucleus may be seen in what appears to be amitotic division. A number of the cells also are bi- and multinucleate. However, multiplication of specific interstitial cells is evidently exceptional. These cells arise directly through modification in shape, and growth from the fusiform and irregular connective tissue cells of the stroma. Moreover, this process seems to be reversible. They thus represent a transient phase in the life of certain cells of the intertubular connective tissue. Their cytoplasm contains

crystalloids,[7] mitochondria and fatty granules. The nature of the lipoid granules is discussed by Whitehead.[8] These cells increase in number during senile atrophy of the testis, but later entirely disappear. They are said to be relatively larger and more abundant also in the testes of tuberculous patients where there may be considerable degeneration and a general infantile condition of the seminal epithelium. Various functions have been ascribed to them—that is, those obviously dependent upon the internal secretion (androsterone, testosterone) of the testes—prominently, origin and maintenance of secondary sexual characters, and basis of sexual instinct. Obviously other cells of the testis might conceivably subserve these func-
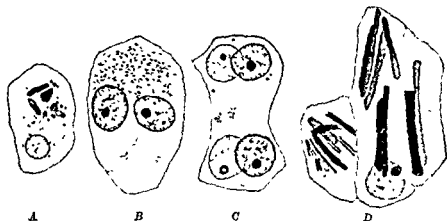
FIG 440—INTERSTITIAL CELLS FROM THE HUMAN TESTIS.

A, B, and *C,* from a twenty-five-year-old man; *A,* shows the idiosome, bacillary centrosomes, lipoid granules and crystalloids; *B,* with two nuclei; *C,* with four nuclei (probably the result of amitotic division) and eight centrosomes *D,* from a forty-one-year-old man, showing large and small crystalloids Highly magnified. (Winiwarter.)

tions, namely, the sustentacular cells and the sex cells. Observations on testes of mules (infertile) and cryptorchid horses, and the findings of Whitehead[9] in a third abdominal testicle of a horse where only interstitial cells in great abundance persisted in normal condition, would seem to relegate these functions to the interstitial cells.

Kingsbury's[10] careful studies of the interstitial cells of the ovary of the cat (elements presumably homologous with the interstitial cells of the testis) strongly support the interpretation of these cells in terms of absorbers of degenerating and disintegrating materials In the ovary all of the earliest and many of the later primary oocytes disintegrate. In the vicinity of such *atretic follicles* interstitial cells laden with lipoid débris are abundant. Their presence, however, is transient, and their number reciprocal to the number of degenerating follicles. This observation, reasoning by analogy, would explain their abundance in the testes of cryptorchid horses, mules, and in the third abdominal testicle; for here also degenerative processes are going on among the sex cells. Testicles of cryptorchid horses and mules are characterized by an unusual *abundance of interstitial* cells, and degeneration of sex cells. These animals experience heat, but are infertile; this

[7] Winiwarter, 1912.
[8] Whitehead, 1912
[9] Whitehead, 1908.
[10] Kingsbury, 1914.

was true also of the stallion from whom two testicles had been removed and in whom subsequently the third abdominal testicle was discovered These observations would seem to indicate that the sexual instinct depends upon an internal secretion on the part of the interstitial cells. The two results can be harmonized on this basis: The internal secretion may actually be formed by the cells of the seminiferous tubules; when these degenerate the products are removed by the interstitial cells; since even in healthy testes there is some degeneration of sex cells, all testes contain a few interstitial cells; these are more abundant at puberty; the secretory products of degenerating sex cells are included among the débris removed by the interstitial cells from which they may be passed into the capillaries of the testicular stroma.

The suggestion that the interstitial cells are in some way connected with secondary sex characters seems disproved by various castration experiments. For example, the spayed hen takes on male secondary sexual characters; if these were dependent exclusively upon the interstitial cells of the testis, they could not appear in the absence of both ovaries and testes.

The experiments of Steinach [11] cannot be ignored in this connection. Steinach made reciprocal transplantations of testes and ovaries in young male and female rats and in guinea-pigs, and claims to have succeeded in changing a potential female, from the viewpoint of secondary sex characters (both physical and temperamental), into a male, and *vice versa*. A male is said to have developed functional mammary glands, and even to have suckled young. Steinach interprets his results to mean that not only do the secondary sex characters of the male and female depend upon the presence of the "pubertal gland" (interstitial cells), but also the fact whether the undifferentiated gonad shall develop into a testis or an ovary. Microscopic examination of the transplant showed that everything suffered degeneration except the interstitial tissue, which underwent extensive hyperplasia. For further information on this and related subjects reference should be made to Allen's *Sex and Internal Secretions*, Williams and Wilkins, 1939.

The Duct System

Tubuli Recti.—At the apex of the testicular lobule the tortuous seminiferous tubules pass into the rete testis of the mediastinum. At this point the tubule becomes straight and is abruptly narrowed. Thus the short straight tubules, tubuli recti, are formed. In the straight tubules the stratified epithelium of the tortuous portions is abruptly exchanged for a very low columnar or flattened type of epithelium with which the Sertoli cells of the tortuous tubules seem to be continuous. The straight tubules are very short and are soon transformed into the irregular anastomosing canals of the rete testis.

Rete Testis.—The connective tissue of the mediastinum is permeated by a network of irregular channels of varying diameter which present frequent dilatations and often have the appearance of broad cleft-like spaces. These are the canals of the rete testis which form a dense network of anastomosing channels. On the one hand they receive the straight tubules, and on the other they pass into the ductuli efferentes, which convey the secretion onward to the globus major (caput) of the epididymis.

The canals of the rete testis are lined with cuboidal or flattened epithelium, which rests upon a delicate basement membrane. This in turn is supported by the connective tissue of the mediastinum The broad but irregular lumen of the

[11] Steinach, 1913

canals is occupied by the secretion from the seminiferous tubules and contains many spermatozoa.

Ductuli Efferentes.—As the tubules of the rete testis leave the mediastinum they are abruptly transformed into peculiar efferent ducts, 10 to 15 in number,
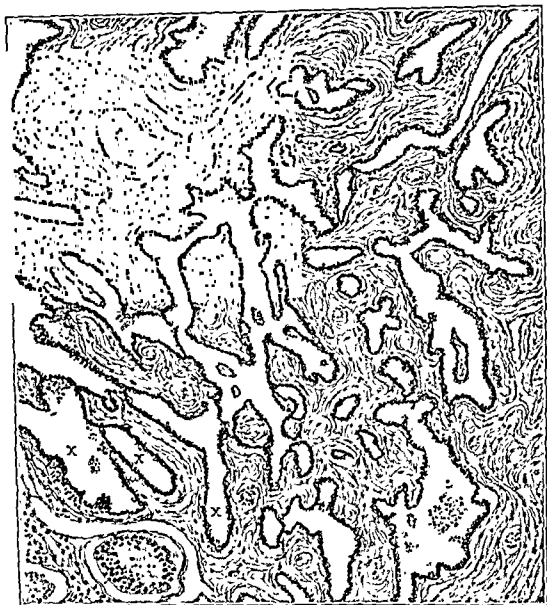
FIG 441.—SECTION OF RETE REGION OF HUMAN TESTIS.

In the lower left-hand corner appears a tubulus contortus; above this are three tubuli recti (X). ×92.

which pass into the globus major of the epididymis and by means of spiral windings form conical masses, *coni vasculosi*, whose apex projects into the *globus major*. The epithelium of these tubules is peculiar in that it contains two varieties of cells, and in that it is thrown into many prominent longitudinal folds or rugae.

In the lining epithelium there are short columnar cells which rest upon the

basement membrane and carry upon their free ends a tuft of short cilia. These cells have an ovoid nucleus and a very finely granular, eosinophil cytoplasm. Between and among the ciliated cells are many broad columnar or polyhedral cells, having remarkably clear cytoplasm, which chiefly occur between and at the base of the rugae, and are frequently arranged in small groups simulating minute secreting glands. These clear cells have spheroidal nuclei and their cytoplasm is filled with large coarse granules. They are quite characteristic of this portion of the excretory tubules of the testis. The *coni vasculosi* form a considerable portion of the globus major of the epididymis. The epithelium rests upon a well-developed basement membrane, outside of which is a robust layer of circularly disposed, smooth muscle cells with intermingled elastic fibers. The nuclei of the lining cells can frequently be seen in some stage of amitotic division.

Epididymis.—The ductus epididymidis forms a long coiled tubule whose convolutions, by their regular cylindrical form and their tall ciliated epithelium, are

sharply distinguished from those of the ductuli efferentes, which have much thinner walls. The lining epithelium of the epididymis is of the tall, ciliated, simple columnar type with elongated ovoid nuclei, a finely granular cytoplasm, and a group of nonmotile cilia which often adhere together to form a peculiar tuft or cluster (brush border). At the base of the ciliated cells is an incomplete layer of basal epithelium, whose flattened cuboidal elements are wedged between the bases of the tall columnar cells. The two-layered epithelium is thus of the pseudostratified type. The

FIG. 442.—A SMALL PORTION OF THE WALL OF AN EFFERENT DUCTULE OF THE TESTICLE.

d, glands in longitudinal section; *d'*, the same in oblique section, *F*, ciliated epithelium, ×140. (Kölliker)

cells apparently multiply largely by amitosis.

The epithelium rests upon a cellular basement membrane, which is supported by a connective tissue tunic of varying thickness. In addition to many elastic fibers, this coat contains a few smooth muscle cells. The coils of the epididymis are firmly united into a solid mass by means of the dense intervening connective tissue. They form the whole of the globus minor and a considerable portion of the globus major. When unraveled the duct of the epididymis measures about twenty feet in length.

Ductus Deferens (Vas Deferens).—This duct is a continuation of the epididymis, whose course now becomes relatively straight. It measures about eighteen inches in length. In this portion of the excretory duct of the testis the lining epithelium soon loses its cilia, and the basal cells become more prominent. Hence in the greater portion of its course the ductus deferens is lined with tall, columnar, nonciliated epithelium, with low basal cells between the attached ends of the columnar cells.

The epithelium rests upon a fibrocellular basement membrane, which is sup-

ported by a fibrous lamina propria. This, in turn, passes almost insensibly into the muscular coat which consists of two layers, an inner circular and an outer longitudinal, both of which are highly developed. In the lower portions of the *ductus deferens*, a thin internal layer of longitudinal smooth muscle fibers is also found.

The fibers of the internal and middle circular layers are frequently less regularly arranged, in which case their oblique bundles interlace with one another
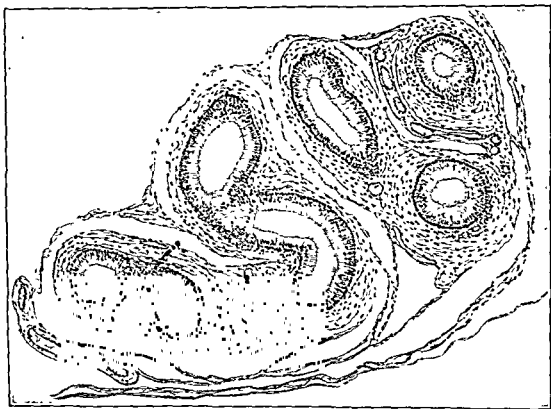
FIG. 443—TRANSECTION OF DUCTUS EPIDIDYMIDIS OF MAN. ×365

in a most intricate manner. The very thick, smooth muscular coat and the relatively narrow lumen give this portion of the duct a firm consistence and a cord-like feel.

In its ampulla—the dilated portion near its prostatic termination—the mucous membrane of the ductus deferens is more loosely attached and the folds or rugae, which elsewhere are few in number, are here very pronounced. The lumen of the ampulla is broad, but elsewhere the lumen of the duct is narrow, as compared with its exceptionally thick muscular wall. As elsewhere in the excretory canal of the testicle, the lumen of the ductus deferens contains a great many of the spermatozoa.

Spermatic Cord.—The spermatic cord in its scrotal portion, in addition to the ductus deferens, contains a mass of connective tissue in which are embedded the smooth muscle fibers of the internal cremaster muscle, the spermatic artery, veins, and nerve plexus, and the vessels of the pampiniform plexus. Closely associated

with these constituents is also the striated cremaster muscle proper. The whole is invested by a reflection of the tunica vaginalis.

The *pampiniform plexus* is a considerable group of venous spaces, usually completely collapsed after death, which are characterized by very thick, firm, fibromuscular walls. The vessels are embedded in dense connective tissue, and the whole plexus in general appearance somewhat resembles the erectile tissues.

FIG. 444.—PORTION OF WALL OF EPIDIDYMIS SHOWING LINING OF TALL COLUMNAR CILIATED EPITHELIUM. ×700.

Seminal Vesicles.—The walls of the seminal vesicles consist of a thin outermost coat of connective tissue in which are many small ganglia, a muscular coat similar to that of the ductus deferens but much thinner, and a characteristic mucosa. The lamina propria of the mucous membrane is a thin layer of delicate cellular connective tissue which loosely attaches the lining epithelium to the muscular coat. The surface of the mucosa presents numerous folds which not only form longitudinal rugae but also possess an intricate network of secondary ridges which are both longitudinal and transverse in direction. This peculiar arrangement results in the appearance of diverticula of various forms and sizes which, except that their epithelium does not differ from that of the surface, might often be interpreted, when seen in section, as representing secondary secreting glands within the mucosa. Slender processes of the corium extend into all the folds of the mucous membrane.

The lining epithelium of the seminal vesicles is of the columnar type and

usually contains but a single layer of cells. Occasionally basal cells are also found in the deeper part of the epithelial layer; in such case the epithelium may be said to be of the pseudostratified type. This variation may possibly be partly dependent upon the distention or relaxation of the vesicles. The cells of the epithelium contain peculiar granules of yellowish pigment which are present in considerable numbers and are quite characteristic of the organ. The superficial cells appear to
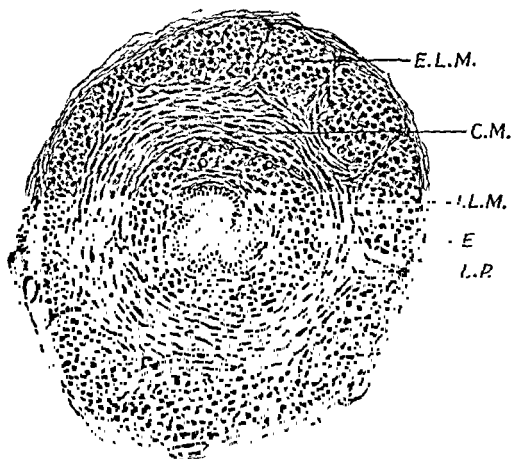
FIG. 445—TRANSECTION OF LOWER PORTION OF DUCTUS DEFERENS OF MAN.

E L M, external longitudinal muscle layer; C M, middle circular muscle layer; I. L. M., internal longitudinal muscle layer; L. P., lamina propria; E, epithelium.

be readily desquamated, and together with coarse granules of secretion form the chief contents of the lumen. Occasional small concretions of irregular form, and homogeneous or lamellar structure, similar to those of the prostate gland, are also found. The seminal vesicles usually contain but few spermatozoa. Occasionally these are present in large numbers; at other times they may be entirely absent. The chief function of the seminal vesicles is now thought to be secretory. Seminal vesicles vary greatly in size and form in different species. They are very large in the hedgehog. They are absent in the carnivora and the marsupalia.

Ejaculatory Ducts.—These ducts are formed by the union of the ampulla of a ductus deferens and the duct of a seminal vesicle and are similar in structure to the ampullae of which they are the continuation. The ejaculatory ducts, how-

with these constituents is also the striated cremaster muscle proper. The whole is invested by a reflection of the tunica vaginalis.

The *pampiniform plexus* is a considerable group of venous spaces, usually completely collapsed after death, which are characterized by very thick, firm, fibromuscular walls. The vessels are embedded in dense connective tissue, and the whole plexus in general appearance somewhat resembles the erectile tissues.

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The lining epithelium of the seminal vesicles is of the columnar type and

FIG 447—SEVERAL ALVEOLI OF THE HUMAN PROSTATE GLAND, SEEN IN SECTION.
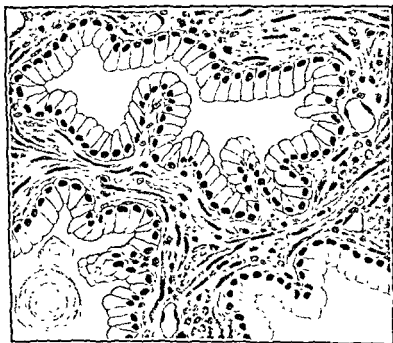
FIG. 448—ADJACENT ALVEOLI OF HUMAN PROSTATE GLAND SHOWING LINING OF TALL
COLUMNAR EPITHELIUM ×500 (Hardesty.)

ever, possess a thinner wall and their mucosa presents the same folded condition as in the seminal vesicles, but to a lesser degree. In its prostatic portion the musculature of the ductus deferens blends with the muscular stroma of the prostate, so that in the ejaculatory duct the smooth muscle no longer forms a distinctly lamellated coat. On approaching the urethra, the epithelium of the ejaculatory ducts presents a gradual transition to the stratified epithelium of the urethral canal.

Associated Glands

Prostate Gland.—This is a compound tubulo-alveolar gland consisting of from 30 to 50 lobules investing the urethra and the ejaculatory ducts. It pours its serous secretion, which has a characteristic odor, into the neighboring portion of the urethra by means of two large and many (15 to 30) small ducts. These open either directly into the urethral canal or indirectly through the utriculus prostaticus (sinus pocularis). The secreting alveoli are embedded in a very dense fibro-muscular *stroma* which, at the surface of the organ, forms an unusually thick *capsule* in which interlacing bundles of smooth muscle are most prominent. This portion of the stroma also contains intrinsic striated muscle fibers in limited numbers. Broad bands of fibro-muscular tissue pass inward from the capsule and form a network of thick septa in the meshes of which are the glandular alveoli. These septa converge toward the urethra, which penetrates the ventral portion of the organ. The muscular fibers of the septa finally blend with the sphincter fibers of the prostatic portion of this canal.

FIG. 446.—MODEL OF A RE-CONSTRUCTED PROSTATE GLAND OF MAN.

The figure includes one lobule. The narrow duct expands and terminates in a large number of alveoli of very varied size and form. ×40. (Maziarski)

The stroma consists of smooth muscle and connective tissue; their fibers are intimately blended. The muscle and connective tissue constitute each about one-fourth of the organ. The muscle cells form either groups or bundles of variable size, or are frequently isolated within the meshes of the connective tissue. Their extreme abundance—in some parts exceeding the connective tissue in volume—is characteristic of the prostatic stroma. The connective tissue, which is sparingly supplied with elastic fibers, is rich in cells. Near the secreting alveoli the muscle fibers are absent and the cellular connective tissue becomes more prominent.

The lining cells of the alveoli are of the tall columnar type, sometimes forming a single, sometimes a multiple, cell layer. They possess spherical or ovoid nuclei

which lie in their deepest third. Their cytoplasm is finely granular and often contains small yellowish granules. The epithelium rests upon a prominent membrana propria, composed of peculiar coarse collagenous fibers, B-collagenous fibers somewhat resembling, but not identical with, reticulum. This type of fiber is present also throughout the stroma and distinguishable by the Bielschowsky technic from the usual collagenous (A-collagenous) fibers.[12]

The epithelium of the alveoli is remarkably folded upon itself, the narrow interval between the two layers of the epithelial folds being always occupied by delicate extensions of the connective tissue stroma. The prominence of the folds varies greatly in different tubules, some showing scarcely any such, the lumen of others being subdivided by deep rugae into numerous anastomosing compartments. The amount of folding also varies in different species, being more highly developed in some of the lower mammals, e.g., the dog, than in man.

The lumen of the prostatic tubules is broad, and is beset with numerous alveolar dilatations and shallow diverticula It is usually broader near the blind extremity and diminishes somewhat in diameter toward the duct. The caliber of the lumen also varies greatly in different tubules and is possibly dependent in part upon the state of secretory activity. The contents of the lumen include the granular albuminous secretion, desquamated epithelial cells, and, as age advances, many so-called *prostatic concretions* (corpora amylacea, prostatic calculi). The concretions vary greatly in size (10 μ to 1 millimeter in diameter), and may be homogeneous, but more frequently present a distinctly lamellated appearance. Prostatic concretions may occur at all ages but increase both in number and size in later life. Occasionally they attain a large size and may become encysted.

FIG. 451.— RECONSTRUCTION OF A BULBO-URETHRAL (COWPER'S) GLAND OF MAN.

The tubular ducts are closely surrounded by the expanded alveoli ×100 (Maziarski)

The prostatic ducts are lined with either a single or a pseudostratified layer of columnar epithelium, and, except for their narrower caliber and more regular contour, they closely resemble the secreting tubules. As the ducts approach their termination their epithelium increases the number of its cell layers The larger ducts, just prior to their termination, are lined with transitional epithelium similar to that of the urethra, into which they open

Blood and Lymph Supply—The prostate gland possesses a rich blood supply. Its larger vessels are found in the capsule, whence they send branches into all portions of the fibromuscular stroma. and form a rich capillary plexus in the connective tissue layer about the epithelium of the secreting alveoli, and a second plexus in the substance of the stroma itself The prostate is abundantly supplied,

[12] Ferguson, 1911

FIG. 449.—PORTION OF PROSTATE GLAND OF AN OLD MAN, SHOWING THE PROSTATIC CONCRETIONS.

In the upper right-hand concretion the concentric lamellae are clearly discernible.
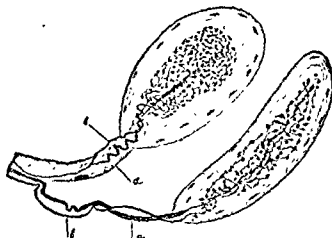
FIG 450.—PROSTATIC GENITAL CORPUSCLES.

a, axial nerve fiber; *b*, periaxial nerve fiber. Methylene blue. Moderately magnified. (After Timofejew)

layer of columnar cells Their wall is supplied with smooth muscle, most of whose fibers have a longitudinal direction. The two ducts of Cowper's glands open into the bulbous portion of the urethra.

Associated Vestigial Structures

The vestigial structures associated with the male reproductive system include the appendices of the testis and epididymis, the superior and inferior ductuli aberrantes, the paradidymis and the sinus pocularis. Of these it may be said in general that they are more or less variable with respect to gross and microscopic structure and even with respect to

FIG 453.—DIAGRAMMATIC REPRESENTATION OF THE VESTIGIAL STRUCTURES OF THE INTERNAL GENITAL SYSTEM OF THE MALE HUMAN EMBRYO. (Kollmann.)

presence; that they resemble histologically the structures with which they are homologous, and that they tend to become cystic.

The *appendix testis* is the least variable of the vestigial associates. It is present in about 90 per cent of cases. It is a small spherical, frequently pedunculated, sac attached to the superior pole of the testis It is covered with tunica vaginalis and lined with simple columnar epithelium, sometimes ciliated, and represents the distal end of the degenerated fetal mullerian duct

The *appendix epididymidis* is a very similar pedunculated structure, much less frequently present. It is situated on the globus major of the epididymis. It is supposed to represent a degenerated wolffian tubule. By some it is regarded as the atrophic distal end of the wolffian duct

The *ductuli aberrantes* are blind tubules, the remnants of mesonephric tubules which failed of inclusion among the ductuli efferentes of the globus major. The superior ductule *opens into the epididymis below the globus major*, the inferior opens at the globus minor; both lie between the testis and the epididymis. They are lined with a single layer of columnar epithelium, sometimes ciliated. The inferior ductule is the more generally present, and has a length of about five centimeters.

The *paradidymis* (organ of Giraldès) lies within the spermatic cord between the head

also, with lymphatic vessels, which are connected with the deep pelvic lymph nodes.

The capsule of the prostate, as also the neighboring connective tissue, both in relation with this organ and with the adjacent seminal vesicles, contains many nerve trunks, chiefly sympathetic, and small ganglia. The latter are especially numerous. In this region a peculiar variety of special nerve ending is found. It was formerly regarded as a pacinian corpuscle, but differs somewhat from these bodies. It perhaps more nearly resembles the *genital corpuscles.* These bodies are
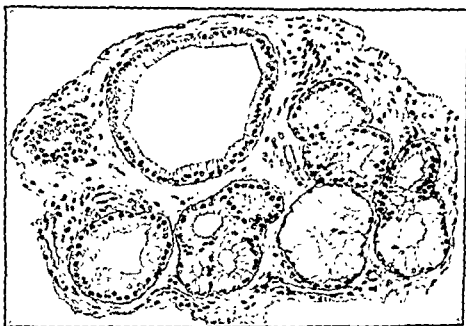
FIG 452.—SECTION OF A LOBULE OF THE BULBO-URETHRAL (COWPER'S) GLAND OF A TWENTY-THREE-YEAR-OLD MAN, SHOWING DUCT (ABOVE) AND TUBULES AT VARIOUS STAGES OF SECRETION. ×250 (Stieve)

distinctly lamellated and possess a broad axial nerve fiber which somewhat resembles that of the end-bulbs of Krause. This nerve fiber is, however, accompanied by another and finer fiber which, as Timofejew [13] has shown, breaks into a close network of fine fibrils surrounding the axial nerve fiber in a peculiar basket-like manner

Bulbo-urethral Glands (Cowper's Glands).—These are two small tubulo-acinose mucus-secreting glands which are divisible into numerous small lobules. The lobules are separated by connective tissue septa containing both smooth and striated muscle fibers. The latter are continuous with the adjacent compressor urethrae muscle The secreting acini are lined with columnar cells, some of which are finely granular and stain with eosin and acid dyes, while others are apparently filled with mucous secretion and react to the specific dyes for mucin Certain other tubular alveoli are lined with low cuboidal or flattened epithelium. The epithelium rests upon a distinct cellular basement membrane.

The interlobular and the smaller intralobular ducts are also lined by a single

13 Timofejew, 1896.

layer of columnar cells Their wall is supplied with smooth muscle, most of whose fibers have a longitudinal direction. The two ducts of Cowper's glands open into the bulbous portion of the urethra.

Associated Vestigial Structures

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Fig 453—Diagrammatic Representation of the Vestigial Structures of the Internal Genital System of the Male Human Embryo. (Kollmann.)

presence; that they resemble histologically the structures with which they are homologous, and that they tend to become cystic.

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The *paradidymis* (organ of Giraldès) lies within the spermatic cord between the head

of the epididymis and the pampiniform plexus. It consists of a variable number of irregular branching tubules, blind at both ends, and lined with a single layer of columnar, ciliated epithelium. These tubules also represent persisting rudimentary mesonephric tubules.

The *sinus pocularis* (sinus prostaticus, vagina masculina) represents the remnant of the proximally fused degenerated fetal müllerian ducts. It is the homologue of the vagina
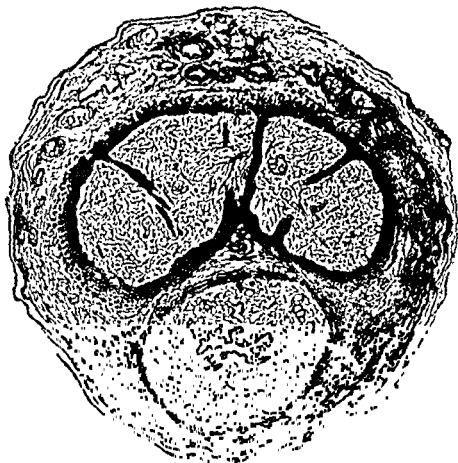
FIG. 454.—TRANSVERSE SECTION THROUGH BODY OF PENIS OF CHILD.

The two corpora cavernosa penis and the corpus cavernosum urethrae, with their investing tunica albuginea, are shown. In the areolar connective tissue of the dorsal surface are shown the dorsal vein, the dorsal arteries and the dorsal nerves. The cutaneous surface is not included. ×125.

in the female. It is a shallow, blind pocket opening into the floor of the prostatic portion of the urethra. It may be bifid distally, varies in length from six to twelve millimeters, and is lined with a columnar epithelium which may be locally ciliated.

EXTERNAL GENITAL ORGAN

Penis.—The penis consists of three masses of erectile tissue, the two *corpora cavernosa penis* and the *corpus spongiosum* or *corpus cavernosum urethrae*, which are firmly united by dense fibrous and areolar connective tissue. The outer cutaneous surface is loosely attached over the body of the organ; its structure does not differ materially from that of the skin of other parts. The subcutaneous tissue is

remarkable for the extreme looseness of its areolae and the absence of fat. In the glans penis the epithelial covering, which is continuous with the preputial epidermis, is firmly united to the underlying erectile tissue.

Each corpus cavernosum is invested with a thick sheath of very dense fibro-elastic tissue, the *tunica albuginea*, divisible into an inner circular and an outer longitudinal layer of fibers, and imperfect between the two corpora cavernosa penis where it forms the *pectiniform septum*. From the inner surface of this fibrous coat connective tissue septa, the trabeculae, pass in all directions and form a reticular framework whose fibrous bands contain many smooth muscle fibers. In the meshes of this framework are characteristic broad venous sinuses which possess no true wall other than their endothelial lining. In the flaccid condition of the organ the blood sinuses are completely collapsed, their walls are in contact, and their lumina almost obliterated, which gives them the appearance of mere slits in the dense connective tissue of the cavernous body When distended by injection, or, in the erectile condition of the organ, by blood, these spaces become widely dilated and form true blood sinuses of broad caliber.

FIG. 455—HELICINE ARTERY IN SECTION, FROM THE URETHRAL BULB OF MAN.

a, lumen of a helicine artery; *b,* fibrous bands of the erectile tissue; *c,c,* lumen of a venous blood space; *m,* opening of the helicine artery into the blood space, *ms,* muscular coat of the artery. Hematoxylin and eosin. ×180 (Kölliker.)

The blood supply of the erectile tissue is peculiar. The arteries terminate either (1) in capillaries, (2) by direct anastomosis with the venules, or (3) by opening directly into the venous sinuses, in which case the minute terminal arterioles have a peculiar looped appearance and were described by J. Müller (1835) as *helicine arteries*. The capillaries form a superficial plexus beneath the tunica albuginea, which opens into a deeper plexus of broader vessels from which the venules take origin Blood following this course through the capillaries and into the venules may not enter the venous sinuses—a direction which is assumed by the greater portion of the blood in the flaccid condition of the organ. The deeper venous plexus communicates freely with the venous sinuses so that the least obstruction to the usual venous outflow diverts the circulation through these channels.

The helicine arteries are confined to the corpora cavernosa penis, where they are most abundant near the root of the organ. The arterioles from which they are derived end by arborization in the connective tissue framework, their terminal twigs entering fibrous processes which project into the venous sinuses. These processes are frequently bound down by delicate fibrous bands which unite their extremity to the wall of the sinus and *produce the characteristic looped condition* when the villus-like projection is distended by the injection of its

arteriole. When partially injected the helicine arteries appear to end blindly, but when completely distended they pour their contents into the venous sinuses.

The venous spaces at the periphery of the erectile body are relatively narrow and the intervening trabeculae are thick. Toward the axis of the body the sinuses become broader and occupy a relatively greater portion of the tissue. Here, also, their long axis, except in the corpus spongiosum, frequently lies in the transverse

THE ERECTILE TISSUE OF THE PENIS.

c r, peripheral capillary plexus; *t a.*, tunica albuginea; *v.s.*, venous spaces; *s*, bands of smooth muscle and vascular connective tissue. ×30. (Kölliker.)

axis of the penis. Both the arteries and the veins of the erectile tissue possess very thick muscular walls, and in both, the intima becomes locally thickened by accumulations of longitudinal muscles and elastic tissue bulging into the lumen. These modifications are less pronounced in the veins than in the arteries.

The tunica albuginea and trabeculae of the corpus spongiosum (corpus cavernosum urethrae) are formed by less dense connective tissue than is found in the corpora cavernosa penis, and their venous spaces are not so broad. The broad anterior end of the corpus spongiosum forms almost the entire body of the glans penis, being only indented beneath the corona by the conical anterior ends of the corpora cavernosa penis which in this part are blended together to form a single median mass. The urethral canal occupies the axis of the corpus spongiosum from its bulb forward to the urinary meatus at the tip of the glans penis. This canal has already been described in the preceding chapter. It should be recalled that its lining epithelium differs in the several segments, being transitional in its prostatic portion, and stratified columnar throughout the membranous and

greater length of the spongy portions, changing to stratified squamous in the dilated fossa navicularis of the glans penis.

The skin of the glans penis is peculiar in the relatively moist character of its epidermis and the consequent imperfect development of its superficial horny layer. Its dermal papillae are conspicuously developed. In the region of the corona the derma contains a ring of large sebaceous glands, the *preputial glands*, which open on the free epithelial surface. Their secretion forms the *smegma*, a peculiarly odoriferous sebum. The so-called glands of Tyson are shallow, nonglandular epithelial pockets opening near the frenulum preputii (Lewis).

The myelinated sensory nerves (dorsal nerves of the penis; branches of the pudic) are abundantly supplied with special nerve end-organs. In the skin they form free varicose endings among the epithelial cells, and are connected with tactile corpuscles of Meissner in the dermal papillae. Deeper in the skin are many end-bulbs of Krause, while still deeper are the peculiar genital corpuscles. Naked fibrils pass to the mucosa of the urethra. Pacinian corpuscles also are found in the loose connective tissue and in the tunica albuginea of the corpora cavernosa. Sympathetic nerve fibers are abundantly supplied to the walls of the blood vessels and to the smooth muscle of the erectile tissue. Branches from the third and fourth sacral nerves also enter the penis as the *nervi erigentes,* supposed to convey the impulse to erection as vasodilator fibers.

The lymphatics of the penis form an abundant superficial set in the subcutaneous tissue; these follow the larger blood vessels and empty into the inguinal lymph nodes. A less abundant deep set of lymphatics in the erectile tissue accompanies the blood vessels of these parts; it drains into the pelvic lymph nodes.

FEMALE ORGANS OF REPRODUCTION

This system includes the ovaries, uterine tubes (oviducts), uterus, vagina, and external genitals. All of these organs are concerned in the reproductive function, the ovary producing the germ cell or ovum, and the uterine tubes providing a suitable site for its maturation and fertilization and the uterus for the later development of the resulting embryo.

INTERNAL GENITAL ORGANS

The Ovary

The ovary also is properly regarded as a gland with a double function, namely cytogenic and endocrine. The specific cells involved in the production of the internal secretion (exclusive of the lutein substance) *are in doubt.* As in the testis, the possibilities include the germ cells, and the interstitial tissue.

Allen and Doisy [14] have demonstrated the *presence of a definite hormone* (thelin, theelol, folliculin, estrin) in the liquor folliculi of the graafian follicles, which stimulates the development of the sex instinct and apparently also the

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[14] Allen and Doisy, 1923.

arteriole. When partially injected the helicine arteries appear to end blindly, but when completely distended they pour their contents into the venous sinuses.

The venous spaces at the periphery of the erectile body are relatively narrow and the intervening trabeculae are thick. Toward the axis of the body the sinuses become broader and occupy a relatively greater portion of the tissue. Here, also, their long axis, except in the corpus spongiosum, frequently lies in the transverse

FIG. 456.—THE ERECTILE TISSUE OF THE PENIS.

c.r., peripheral capillary plexus; *t a.,* tunica albuginea; *v.s.,* venous spaces; *z,* bands of smooth muscle and vascular connective tissue. ×30. (Kölliker.)

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portions of the medulla and is in turn clothed by a layer of *germinal epithelium*, a continuation of the peritoneal epithelium. The cells of the peritoneum in this area are peculiar in that they possess a typically cuboidal shape, and are thus sharply distinguished from the flattened mesothelial cells of the surrounding portions of the peritoneum.

Medulla.—The medulla of the ovary consists of a fibromuscular stroma and large numbers of blood vessels. Its arteries are characterized by their spirally tortuous course and thick muscular walls; its veins are numerous and large, and their endothelium rests almost directly upon the fibromuscular stroma. This portion of the ovarian stroma consists of fibrous connective tissue in which are elastic fibers and considerable numbers of smooth muscle cells. The connective tissue is richly supplied with cellular elements, most of which are ovoid or fusiform in shape.

Cortex.—The cortex of the ovary likewise contains a vascular stroma and also large numbers of ova which are in all stages of development, from the genetic cells of the germinal epithelium up to the more mature germ cells, contained within epithelial sacs and known as *ovarian follicles*. During the menstrual epoch the ovaries also contain peculiar yellowish bodies, *corpora lutea*, resulting from the rupture of the largest follicles, a phenomenon which marks the climax of the process of ovulation.

The stroma of the ovarian cortex is a connective tissue structure which contains relatively few elastic fibers and, except near the medulla, very little if any smooth muscle. It is, however, abundantly supplied with connective tissue cells of large size, most of which are ovoid, fusiform, or even considerably elongated in shape. Many of these cells closely simulate smooth muscle on superficial examination, but are readily distinguished by careful study, especially if specimens are prepared by the various differential staining methods.

In the vicinity of the follicles the stroma is specially rich in cellular elements and is otherwise modified to form a concentric coat for each of these bodies. This coat, the *theca folliculi*, consists of (*a*) an outer layer, or *tunica externa*, composed chiefly of connective tissue whose interlacing bundles are concentrically disposed, (*b*) an inner layer, *tunica interna*, which is peculiarly rich in large ovoid cells, and (*c*) an innermost *membrana propria*, upon which the epithelial cells of the follicle directly rest.

At the surface of the ovary the cortical stroma forms a dense layer of fine connective tissue fibers whose delicate bundles interlace in a close-meshed network. This layer, which immediately underlies the germinal epithelium at the surface of the ovarian cortex, is known as the *tunica albuginea*. It differs greatly in thickness in different mammalian species, in different individuals of the same species, and even in different portions of the same ovary. Its deeper surface blends insensibly with the underlying stroma of the cortex.

The general appearance of the ovary varies according to the number, size, and stage of development of its ova and their follicles. At birth the cortex is packed with large numbers of newly formed ova, all of which are in approxi-

secondary sex characters. Four to six injections of the liquor from hog ovaries into immature female rats (normal or spayed) produced[1] in from 2 to 3 days typical estrual phenomena and mating desire as early as from 20 to 50 days before normal puberty.

The ovary, moreover, periodically elaborates secondary internal secretions. The organ involved is a transitory structure, the *corpus luteum* of pregnancy. This will be described below. Its functions pertain to an inhibition of ovulation during pregnancy and the preparation of the uterine mucosa for proper implantation and
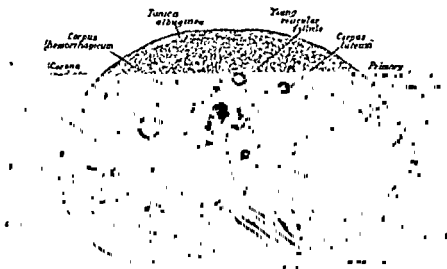
FIG. 457.—SECTION OF OVARY OF ADULT CAT, THROUGH HILUS, SHOWING FIVE VESICULAR (GRAAFIAN) FOLLICLES, WITH THE CUMULUS OOPHORUS AND THE INCLOSED OVUM.

The antrum folliculi is filled with a granular material, a coagulum of the liquor folliculi. Note that the ovarian follicles are in the cortical portion, the medulla containing no follicles. ×7.

normal development of the fertilized ovum. The hormone involved in these reactions has been named *luteosterone, corporin, progesterone* and *progestin;* it is effective only after action of the primary ovarian hormone theelin (Allen). An additional secondary hormone, *relaxin,* has been demonstrated in guinea-pigs by Hisaw (1929). It effects a marked relaxation of the pelvic ligaments and also acts only in succession with theelin (estrone). As shown by extirpation experiments the internal secretions of both ovary and testis influence also the nervous system, and seem essential for normal nervous function.

The ovary is a solid ovoid body, about one and one-half inches long, three-quarters of an inch wide and one-half inch thick. It is attached to the margin of the broad ligament posteriorly by a short, thick connective tissue pedicle, the *mesovarium,* which transmits the blood vessels with which the ovary is richly supplied. At its ovarian attachment the mesovarium becomes continuous with the connective tissue stroma of the ovary. The indentation which is thus produced is known as the *hilus*

The substance of the ovary is divisible into a central medulla which reaches the surface only at the hilus, and a peripheral *cortex* which invests all other

nd the fragments may be transported to the peripheral portions of the cytoplasm, or may be irregularly scattered as small round chromatic granules, which occur throughout the cytoplasm. The physiological interpretation of these bodies is uncertain.

Nucleus.—The nucleus of the ovum is a large spheroidal vesicle, the volume and distribution of whose chromatin is subject to great variation. Chromatin is present in greatest amount during the period of most active cell growth, in which the cytoplasm of the ovum is enormously increased in volume. At this time the

FIG 458—PRIMARY OOCYTE OF OVARIAN FOLLICLE OF DOG, SHOWING ENVELOPING VITELLINE MEMBRANE, ZONA PELLUCIDA (OOLEMMA) AND CELLS OF CORONA RADIATA. (Bonnet)

nucleus often appears as a solid mass of chromatin. Later the chromatin is diminished in volume; portions of its substance being possibly extruded into the surrounding cytoplasm; the nucleus then acquires a characteristic vesicular appearance.

The nuclear membrane is sharply defined and is at most times prominent. The nuclear matrix or nuclear sap abounds in the vesicular type of nucleus and the chromatin is scattered in small particles which adhere to the inner surface of the nuclear wall or to the delicate achromatic linin threads.

Each ovum as a rule contains a single nucleus (germinal vesicle), though occasionally two nuclei occur The latter condition is presumed to arise either by the fusion of two ova within a single follicle or from incomplete cell division during development.

Each nucleus, during its vesicular stage, usually contains a single *nucleolus*, which forms a spherical mass of chromatin, situated, like the nucleus itself, eccentrically rather than centrally The staining properties of the nucleoli vary remarkably. Usually they take the basic (nuclear) dyes to a greater or less depth; occasionally they exhibit an affinity for the acid (cytoplasmic) dyes; still other nucleoli take a metachromatic or irregular tint with the ordinary nuclear stains. Many nuclei lack a nucleolus.

mately the same stage of development. Their number has been estimated at between 30,000 and 70,000. Few, if any, new ova are formed after birth. Since in the normal sexual cycle from puberty to the menopause (from about the thirteenth to the forty-fifth year), a period of about 32 years, only about 400 eggs are liberated, the vast majority of potential ova must degenerate. This process of degeneration is especially active after the climacteric.

During childhood the formation of larger follicles goes forward at an unequal rate, some ova rapidly approaching maturity, others apparently remaining almost stationary, and still others undergoing retrograde development, so that at the age of puberty the ovary contains germ cells and follicles in all stages of development. After puberty the ripe follicles successively rupture and result in the formation of many corpora lutea which promptly degenerate, and are finally replaced by dense connective tissue in the form of small scar-like masses known as the *corpora albicantia.* Hence throughout the menstrual epoch the ovarian cortex contains many corpora lutea and corpora albicantia in addition to ova and follicles in various earlier stages of development. After the climacteric the remaining follicles degenerate and the process of ovulation gradually ceases.

We shall now discuss the structure of the ovum or female *germ cell* and shall then successively trace its development and maturation, the formation of its vesicular (graafian) follicle, the rupture of the follicle, and the subsequent history of the corpus luteum.

The Ovum.—The ovum is a spherical cell of large size (200 to 300 μ). When fully developed it is surrounded by a thick layer of exoplasm, the *zona pellucida,* which is probably derived from the cytoplasm of the follicular epithelium by which the ovum is closely invested. The ovum itself consists of a mass of cytoplasm, the *vitellus,* and a large vesicular *nucleus* or *germinal vesicle,* within which is frequently a single prominent *nucleolus* or *germinal spot.* The cytoplasm of the mature ovum is inclosed by a very delicate cell membrane, known as the *vitelline membrane,* which is not demonstrable in the primitive ova of the younger follicles.

Cytoplasm.—The cytoplasm of the ovum at first appears finely reticular, but as its development advances a fatty material is deposited within its meshes, usually in the form of minute irregular spheroids, by the accumulation of which the reticular cytoplasm is in great part replaced by a granulofatty mass of faint yellowish color known as *deutoplasm.* Frequently this metamorphosis is not quite complete, a remnant of the original cytoplasm persisting beneath the vitelline membrane and in the vicinity of the nucleus.

Numerous cytoplasmic structures have been described in these cells, chief among which are the *accessory nucleus* and the *yolk nucleus.* The accessory nuclei, occasionally chromatinic and therefore basophil, more frequently stain with cytoplasmic dyes and are at times attached, at other times separate from the true nucleus. They are more probably remnants of mitotic spindles. The yolk nuclei of mammalian ova most frequently take the form of crescentic masses of lightly staining chromatin (chromidia) which partially surround the nucleus, forming a so-called *nuclear cap.* They are often found in various stages of disintegration,

and the fragments may be transported to the peripheral portions of the cytoplasm, or may be irregularly scattered as small round chromatic granules, which occur throughout the cytoplasm. The physiological interpretation of these bodies is uncertain.

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Cell of corona radiata

Zona pellucida

Germinal vesicle

Vitelline membrane

Hypolemmal space

Oöcentrum

Fig. 458.—Primary Oöcyte of Ovarian Follicle of Dog, Showing Enveloping Vitelline Membrane, Zona Pellucida (Oölemma) and Cells of Corona Radiata. (Bonnet)

nucleus often appears as a solid mass of chromatin. Later the chromatin is diminished in volume, portions of its substance being possibly extruded into the surrounding cytoplasm; the nucleus then acquires a characteristic vesicular appearance.

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In the development of the ovum from the germinal epithelium, whose cells from their homology with the spermatogonia have been termed *oogonia*, there occur several mitoses which result in so-called *primary oocytes*; these later develop into the mature ovum. At about the time of its extrusion from the ripe follicle a final series of mitoses occur, which distinguish the maturation of the ovum. In this process there is a series of two mitoses which result in the appearance of the polar bodies and produce a *reduction* in the number of chromosomes to one-half the number which is characteristic of the somatic cells. By the first

FIG 459—FROM A SECTION OF THE OVARIAN CORTEX OF A NEWBORN KITTEN.

K, Pflüger's tubes; *Ke*, germinal epithelium; *m*, mitosis; *Str*, ovarian stroma; *Ub*, primitive follicles. Moderately magnified. (Kölliker.)

mitosis the cell produces what may be termed a daughter ovum (*secondary oocyte*) together with the first *polar body*, a minute cell of insignificant size. A second mitosis ensues giving origin to the *mature ovum* or *ootid* and the second polar body. The egg now contains only one-half the specific number of chromosomes The full specific number is restored at fertilization by the addition of the male reduced complement carried by the sperm.

Development of the Ovarian Follicle.—The development of the ovarian follicle goes hand in hand with that of the ovum and can be readily followed in ovaries from individuals of different ages, children and adults, the ripe follicles and corpora lutea appearing only after puberty. During the first five months of fetal life the cuboidal germinative epithelium contributes cells to the core of the gonad. At sexual maturity, about the fourteenth year, the germinative epithelium is a single layer of flattened cells completely investing the gonad. At irregular intervals the epithelium invades the gonad in the form of folds and tubular pockets,

simulating in tangential sections so-called Pflüger's tubes of lower forms. The germ cells and those of the enveloping follicle throughout the fertile life of the human female derive only from the parenchymatous (somatic) part of the gonad, in contrast with conditions as reported in rodents, the cat and the dog, where there is apparently a continuous delivery of cells from the germinative epithelium to augment the resident germ cells, interstitial cells and follicle cells.

FIG 460.—THREE STAGES IN THE DEVELOPMENT OF THE GRAAFIAN FOLLICLE.

A, primary follicle with single layer of enveloping cells, *B*, primary follicle with multiple layers of cells, and beginning of vacuolization; *C*, vesicular follicle, with later stage in formation of antrum folliculi bounded by inner corona radiata and peripheral membrana granulosa. (Hardesty)

Simkins [15] recognized two kinds of follicles in the human ovary at birth: primordial and primary. Primordial follicles have an average diameter of 30 microns, are incompletely enveloped by flat cells, number from 65 to over 143,000 and undergo gradual degeneration and disappear at the onset of sexual maturity. The primary follicles have an average diameter of 50 microns, are completely enveloped by spheric cells, occur in much smaller numbers, which remain fairly constant from birth to sexual maturity. New gonocytes do not represent stored germ cells as previously believed, but according to Simkins are "somatic cells induced to grow into germ cells by the gonad-stimulating hormone of the anterior lobe of the hypophysis."

[15] Simkins, 1932.

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[15] Simkins, 1932.

Many follicles never go beyond this primary stage of development, but after a time undergo retrograde metamorphosis either by gradual atrophy or by a process, known as *atresia* of the follicle. In this process the chromatolysis in the ovum and its surrounding follicular cells is followed by growth and organization of the theca folliculi, the connective tissue which is thus formed finally replacing the atretic follicle.

FIG. 461.—PERIPHERAL AREA OF OVARY OF DOG, SHOWING PRIMARY FOLLICLES AND ONE VESICULAR (GRAAFIAN) FOLLICLE. ×800.

After remaining stationary for a long period, often for years, certain of the primitive follicles enter upon a period of rapid growth. This process first affects the ovum and results in the appearance of the deutoplasm, zona pellucida, and other accessory structures, as already described. Cell multiplication now occurs in the surrounding epithelial cells, so that, instead of the single row of epithelium which surrounds the ovum of the primitive follicle, the ripening follicle soon acquires a layer of follicular epithelium several cells deep. This may be designated the *mantle layer*.

The rapid multiplication of the epithelial cells is soon followed by active secretion, resulting in the formation of a clear fluid by which the cells are more and

more separated, and the cytoplasm of adjacent cells is then readily seen to be firmly joined together by numerous delicate processes which may be regarded as *intercellular bridges.* Similar processes unite the neighboring cells to the zona pellucida which has already formed about the ovum.

The accumulation of the fluid *liquor folliculi* within the follicle soon appears to tear apart certain of the epithelial cells, and a fluid-filled space, the *antrum folliculi*, is thus formed. Such a follicle is known as a *vesicular* or *graafian follicle.* Follicles intermediate between the primary follicles with a single or double layer of mantle cells and vesicular follicles may for convenience be called *intermediate* or *growing* follicles. The epithelial cells are separated by the antrum into two layers: the one, adherent to the membrana propria of the follicle, is known as the *membrana granulosa;* the other, adherent to the zona pellucida of the ovum, is designated the *discus proligerus.* The two layers remain in contact at one point, and as the liquor folliculi increases in volume, the attached discus proligerus with its contained ovum comes to occupy a more and more eccentric position. The cells of the membrana granulosa, where the two layers are in contact, appear to pile up about the ovum in the form of a hillock, the so-called *cumulus oophorus.* The latter term is now generally used exclusively in a sense to include and displace the term discus proligerus.

The cells of the cumulus, which adjoin the zona pellucida, become somewhat elongated and in this way they form a radiate investment consisting of one or two rows of columnar cells which surround the zona pellucida of the ovum and are known as the *corona radiata.* With the increase of the liquor folliculi the cumulus with its contained ovum is soon separated from its attachment to the membrana granulosa and the development of the follicle is complete.

During this period of rapid growth and development the follicle has increased in size from a diameter which scarcely exceeded that of its ovum (about $300\,\mu$) to such a size that it occupies the entire breadth of the ovarian cortex. It is now ready for the final steps in the maturation of its ovum and for the rupture of the follicle.

The forces which lead to the rupture of the follicle are not fully determined. They are undoubtedly multiple. In addition to the gradual attenuation of the layer of cortical stroma which covers the free surface of the follicle and is known as the *stigma*, they include the gradual accumulation of liquor folliculi under increasing tension, and the marked congestion of the ovary at the approach of the menstrual period, which is accompanied by the determination of an undue proportion of blood to the theca of the ripe follicle (Clark). The contraction of the smooth muscle contained in the stroma of the deeper part of the cortex and adjacent portions of the medulla may be an additional factor. In any event, as a result of the independent or combined action of these, or other unknown forces, the follicle ruptures in the direction of least resistance, *viz.*, at the attenuated stigma, and the liquor folliculi gushes forth, carrying with it the detached ovum invested with its cumulus. The ovum is now free to enter the uterine tube and prepare itself for fertilization and the development of the future embryo.

The ovum finds its way from the abdominal cavity into the oviduct by aid of currents established in the direction of the orifice by the cilia of the cells covering the fimbriae; perhaps assisted by a direct grasping activity on the part of the fimbriae.

Since spermatozoa are free to wander out of the uterine tube into the abdominal cavity, and since an egg may occasionally fail to reach the opening of the uterine tube, the possibilities are offered for an abdominal pregnancy, a result occasionally consummated. Likewise an egg may fail to become expelled from its follicle and may then become fertilized within the ovary; or an egg fertilized in the abdominal cavity may perhaps subsequently become implanted in an empty follicle. Development proceeding under such conditions results in an ovarian pregnancy, of which about one hundred cases have now been reported.[16] Ovarian pregnancies cannot proceed normally, and may early call for surgical intervention. Occasionally a follicle may contain more than one ovum, bi- and tri-ovular follicles being common. Such follicles apparently present the possibilities for ordinary twinning and multiple births. Arnold[17] records follicles in the ovary of a negress also with from four to ten oocytes, and one each with eleven and thirteen oocytes.

The following table is offered for the benefit of the student as a résumé of the several structural layers of the ripe graafian follicle. The structures are enumerated in order from without inward:

1. Theca folliculi $\begin{cases} \text{tunica externa} \\ \text{tunica interna} \\ \text{membrana propria} \end{cases}$

2. Membrana granulosa (stratum granulosum)
3. Liquor folliculi—occupying the antrum folliculi
4. Discus proligerus (cumulus oophorus)
5. Corona radiata
6. Zona pellucida (zona striata)
7. Perivitelline space—possibly an artifact
8. Vitelline membrane
9. Vitellus (egg cytoplasm)
10. Nucleus (germinal vesicle)
11. Nucleolus (germinal spot)

Corpus Luteum.—The rupture of the follicle is accompanied by sudden relief of the intrafollicular tension and consequent hemorrhage from the thin-walled capillaries of the theca folliculi. Thus the cavity of the follicle is filled with blood; the ruptured follicle is then known as a *corpus hemorrhagicum.* This is the first stage in the formation of the corpus luteum.

Promptly succeeding the formation of the corpus hemorrhagicum, *lutein cells* appear at the periphery of the body. They are large, ovoid or polyhedral cells having a clear finely granular cytoplasm and a peculiar yellow color due to the presence of a pigment known as *lutein.* Moreover, the cytoplasm of the lutein cells becomes very rapidly infiltrated with droplets of fat, likewise deeply colored by the lutein pigment which is apparently held in solution. The origin of these cells is still a matter of controversy. By certain observers they have been thought to result from the growth and multiplication of those cells of the membrana granulosa which remain after the rupture of the follicle (Bischoff, Pflüger, Sobotta); by

16 Jordan, Garrett and Norfleet, 1932.
17 Arnold, 1912

others they are derived from the connective tissue cells in the tunica interna of the theca folliculi (Kölliker, His, Palladino). Teacher [18] interprets his preparations to "indicate quite clearly that, whatever the source of the cells may be in lower animals, they do not in man arise from the membrana granulosa." Lutein cells may multiply by mitosis. In the pig the corpora lutea are formed chiefly from granulosa cells, in small part also from theca cells.[19]

The lutein cells increase rapidly both in number and in size, and gradually encroach upon the margin of the blood clot whose progressive absorption pre-

FIG. 462—SECTION THROUGH THE PERIPHERAL PORTION OF A CORPUS LUTEUM, SHOWING LUTEIN CELLS

a, the fibrous coat of the corpus luteum; b, lutein cells with bands of newly formed connective tissue, c, central blood clot, partially organized. Moderately magnified. (Williams.)

cedes the advance of the lutein cells. But not only does the lutein mass grow centralward; it also, and especially in the event of fertilization of the discharged ovum with the consequently increased vascularity of the reproductive organs, grows at the periphery and in this way greatly increases the diameter of the corpus luteum.

Minute vascular sprouts of embryonic connective tissue now penetrate the lutein mass from the adjacent stroma of the theca folliculi, and growing centralward in septa-like processes, finally penetrate as far as the central blood clot. Hence the corpus luteum at this stage presents a more or less radiate structure. The central ends of the embryonic connective tissue septa frequently unite to

[18] Teacher, 1908.
[19] Corner, 1919.

Since spermatozoa are free to wander out of the uterine tube into the abdominal cavity, and since an egg may occasionally fail to reach the opening of the uterine tube, the possibilities are offered for an abdominal pregnancy, a result occasionally consummated. Likewise an egg may fail to become expelled from its follicle and may then become fertilized within the ovary; or an egg fertilized in the abdominal cavity may perhaps subsequently become implanted in an empty follicle. Development proceeding under such conditions results in an ovarian pregnancy, of which about one hundred cases have now been reported.[16] Ovarian pregnancies cannot proceed normally, and may early call for surgical intervention. Occasionally a follicle may contain more than one ovum, bi- and tri-ovular follicles being common. Such follicles apparently present the possibilities for ordinary twinning and multiple births. Arnold[17] records follicles in the ovary of a negress also with from four to ten oocytes, and one each with eleven and thirteen oocytes.

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[18] Teacher, 1908.
[19] Corner, 1919.

inclose the remnant of the central blood clot, or by further proliferation they may entirely replace the clot by a mass of newly formed gelatinous connective tissue.

The absorption of the blood clot usually proceeds slowly. Remnants of the disintegrating blood in the form of a central stellate mass, which often contains hematoidin crystals, frequently persist until the corpus luteum has become well organized with connective tissue.
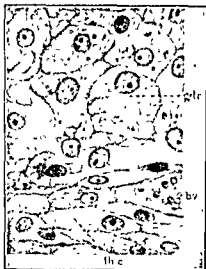
FIG. 463—PORTION OF CORPUS
LUTEUM OF PIG.

Gr.l c, granulosa lutein cells;
th c, theca lutein cells; *b.v.*, blood
vessel. × 1000 (Corner.)

The formation of new connective tissue is followed by its contraction. That this process occurs very early in the connective tissue first formed at the periphery of the body, may possibly be held to account for the fatty infiltration and final degeneration of the lutein cells, because of the consequent interference with their vascular supply.

By continued development the entire mass of lutein cells is gradually replaced by connective tissue, which, by further contraction, finally produces a dense white fibrous *scar*, no longer containing lutein pigment, known as a *corpus albicans* (*candicans*). This body persists for a long period, but undergoes progressive contraction until only a minute scar of almost microscopical size remains to mark the site of the ruptured follicle and the highly developed corpus luteum. Such scars persist for years in the stroma of the ovarian cortex.

Finally it must be stated that there are no recognizable histological differences, other than those of size and duration, between the *corpora lutea vera* of pregnancy and the *corpora lutea spuria* whose formation accompanies the extrusion of the unfertilized ovum. The true corpora lutea are of relatively large size and persist for many months, while the spurious are somewhat smaller and persist for little more than one month. Both pass through the same histological process of development and degeneration and both leave their scars in the substances of the ovarian stroma.

Ovarian scars also arise through atresia of the larger follicles, the degeneration of whose epithelium is followed by an ingrowth of tissue derived from the theca folliculi, and the gradual development, organization, and final contraction of the connective tissue. The process forms, as it were, a minute but imperfect corpus albicans, in the center of which is often the shrunken degenerating remains of the ovum. Certain small acidophilic homogeneous bodies, the so-called Call-Exner bodies, of uncertain significance are also occasionally present in the membrana granulosa of the ovarian follicles.

Aschoff [20] denies the occurrence of a primary *corpus hemorrhagicum*. Hemorrhage is said not to appear at the time of ovulation, except occasionally and then only in small amounts. More abundant hemorrhage into the central cavity

[20] Aschoff, 1924.

of the forming corpus luteum of menstruation (*corpus folliculare menstruationis*) occurs at the first succeeding menses. Blood from invading capillaries mingles with the serous fluid content. The hemosiderin of the central blood clot contributes to the yellow color of the corpus luteum. Aschoff recognizes four successive periods of the *corpus folliculare menstruationis:* the corpus folliculare menstruationis *efflorescens*, the corpus folliculare menstruationis *hemorrhagicum*, the corpus folliculare menstruationis *luteum*, and the corpus folliculare menstruationis *involutum* or *candicans*.

The hilum of the postpubertal ovary contains cells, previously interpreted as para-ganglionar pheochrome elements, which appear more nearly homologous to the inter-stitial cell of Leydig of the testis.[21] These so-called Berger cells do not react positively to histochemical tests for chromaffin granules, nor are they argyrophile. They are ovoid cells, varying in diameter from 7 to 20 microns. The cytoplasm is acidophilic and con-tains abundant lipoid granules and spherules and a variable amount of brown-yellowish pigment granules Amaral[22] regards these cells as the morphological substratum of the secretion of the "masculinizing hormones" in women, which is in accord with modern opinion that the hilum of vertebrate gonads has a masculinizing rôle and the cortex a feminizing rôle.[23]

Blood Supply.—The arterial vessels of the ovary are derived from the branches of the ovarian and uterine arteries. These vessels enter the ovary through the mesovarium and divide into numerous branches which pursue a peculiar spiral
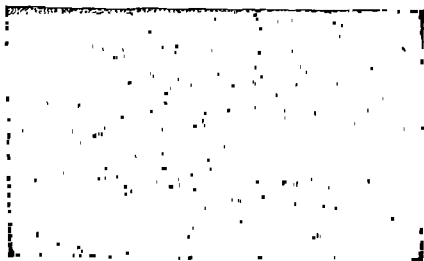
FIG 464.—A CORPUS ALBICANS, FROM A SECTION OF THE HUMAN OVARY. ×75. (Williams.)

or corkscrew course through the stroma of the medulla, and finally enter the cortex. They possess thick muscular walls containing bundles of longitudinal smooth muscle fibers. In the cortex they supply capillaries to the stroma, and

[21] Berger, 1923
[22] Amaral, 1938
[23] Witschi, 1929

in the theca folliculi of the graafian follicles they form rich plexuses of broad capillaries and thin-walled venules. As the follicle approaches maturity these plexuses become enormously developed and apparently bear an important relation to the rupture of the follicle and the rapid development of the corpus luteum. The veins, which take origin from the venules of these capillary plexuses, converge toward the medulla, where they form a plexus of large thin-walled vessels, the *plexus venosus ovarii* or *pampiniform plexus*. This is embedded in the connective tissue of the medulla, the mesovarium, and the adjacent portions of the broad ligament.

The *lymphatics* arise in the cortical stroma by anastomosing canals and capillaries of irregular caliber, which are especially abundant in the walls of the graafian follicles. These vessels converge toward the medulla, where they enter lymphatics which are supplied with valves, and find their way to the lymph nodes of the pelvic and lumbar regions.

The *nerves* are chiefly derived from the ovarian sympathetic plexuses. They enter at the hilus and are distributed to the walls of the blood vessels, and to the stroma of the ovary; here they form a rich terminal plexus in the walls of the follicles. Whether or not the naked fibrils are distributed to the epithelial cells within the follicle has not been satisfactorily determined. The small ganglia of the medulla include also pheochrome cells (Winiwarter); and certain sensory fibers are said to end in lamellar corpuscles.

The Uterine Tube (Oviduct, Fallopian Tube)

The uterine tube is a narrow duct about 4½ inches long, leading from the ovary to the cavity of the uterus. It consists of a broad, funnel-shaped, fringed or *fimbriated extremity* (or infundibulum), a constricted *neck*, an intermediate *ampulla* of considerable diameter, and a slender *isthmus* by which the tube communicates with the uterine cavity.

Throughout the entire tube its wall, which becomes gradually thinner from isthmus to infundibulum, consists of three coats—mucous, muscular and serous —but the character of its mucous membrane differs somewhat in its several portions. In the isthmus it is relatively smooth and usually presents four longitudinal ridges which have *few secondary or accessory folds*; in the ampulla the mucosa is greatly folded, the primary rugae possessing small secondary folds which extend in all directions, and by their very complexity nearly obliterate the otherwise broad lumen. In the fimbriated portion the folds of the mucosa are continued into the fimbriae, at the margin of which the columnar ciliated epithelium of the oviduct becomes *directly continuous with the serous mesothelium* of the peritoneum investing the outer surface of the tube.

The *mucosa* is clothed with columnar epithelium, arranged either in a simple or pseudostratified manner, the greater number of whose cells are provided with cilia. The ciliary motion is directed toward the uterus. The epithelial layer covers all the folds of the mucosa and, extending deeply into the crevices, forms invaginations which, in transections of the tube, simulate glandular structures. There
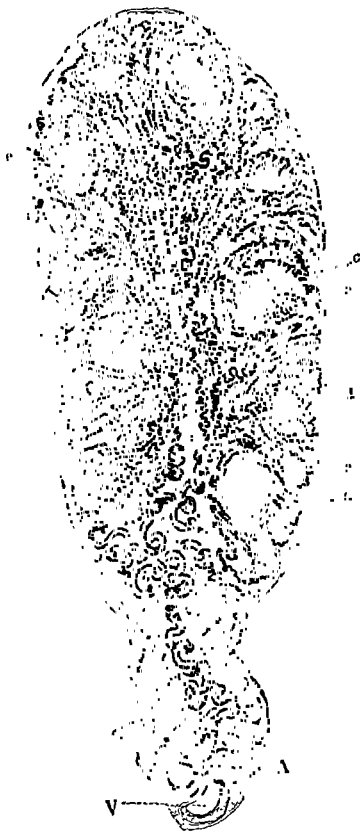
FIG 465.—FROM A THICK SECTION OF THE OVARY OF A WOMAN.

The blood vessels have been injected. *A*, *a*, and *a'*, arteries; *b*, corpus luteum, partially organized; *c*, point where rupture of the follicle occurred; *d*, tangential section of a follicle; *e*, corpora lutea which have organized and are already retrogressive. (Clark.)
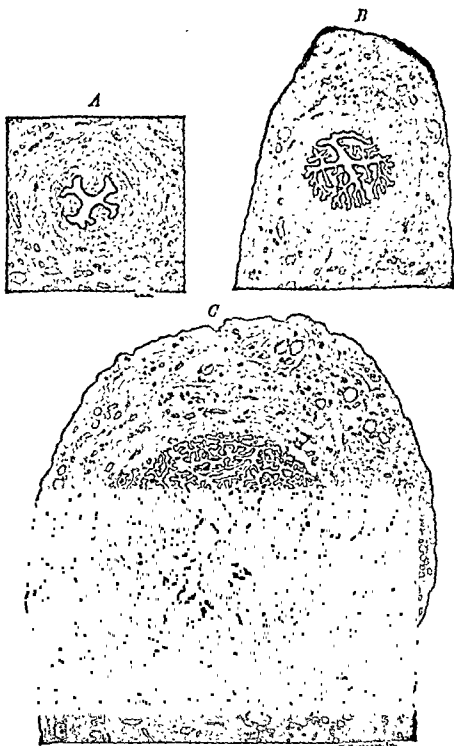
FIG 466—TRANSECTIONS OF THE HUMAN OVIDUCT.
A, uterine; *B*, isthmic, and *C*, ampullar portions. ×15 (Williams.)

are, however, no true secreting glands in the oviduct. Here and there groups of nonciliated cells with clear cytoplasm occur among the more numerous ciliated cells of the mucosa.

The epithelium rests upon a thin homogeneous basement membrane beneath which is a lamina propria consisting of a cellular type of connective tissue. Many of the connective tissue cells are of fusiform shape, and, unless specially stained or carefully examined, they closely resemble smooth muscle cells. The mucosa, however, contains no muscle except at the bases of the largest folds, into which occasional fibers from the adjacent muscular coat penetrate.

FIG 467.—FROM A TRANSECTION OF THE AMPULLA OF THE OVIDUCT, SHOWING THE STRUCTURE OF THE MUCOSA. ×280 (Williams)

The *muscular wall* of the oviduct is formed by two layers of smooth muscle— a broad inner circular layer, and an outer longitudinal coat. The longitudinal layer is very unequally developed at different portions of the circumference, but is relatively thin in all parts, and is entirely wanting at frequent intervals. It is usually broadest at the free margin of the oviduct and at its opposite side where the tube is attached to the broad ligament. The inner circular fibers are more or less obliquely disposed, and, toward the mucosa, the muscular bundles fuse insensibly with the cellular connective tissue of the mucous membrane. In general the inner circular layer is thickest at the isthmus and thinnest at the infundibulum, while the longitudinal layer is thickest toward the fimbriated end.

The *serous coat* of the uterine tube is continuous with the peritoneum. It consists of an outermost layer of mesothelium which rests upon a subepithelial layer of connective tissue, by which it is firmly united to the muscular wall. This por-
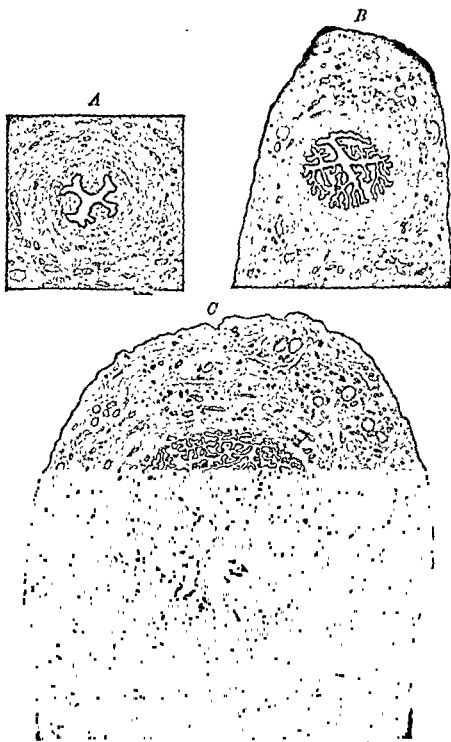
FIG 466.—TRANSECTIONS OF THE HUMAN OVIDUCT.
A, uterine; *B*, isthmic, and *C*, ampullar portions ×15. (Williams)

vessels pass to the serous coat and enter valved lymphatics by which the lymph is conveyed to the lymph nodes of the lumbar region.

The *nerves*, which are chiefly sympathetic, are distributed from a plexus in the serous coat, to the muscular wall, and to the mucosa, in which they form a terminal subepithelial plexus.

The Uterus

The uterus is a hollow pear-shaped organ, divisible into a deepest or *fundus* portion, the *body*, and the *cervix*. It is about 3 inches in depth, 1½ in width and 1 in thickness. The cervix opens into the body through the internal os, into the vagina through the external os. Its wall consists of a mucous membrane, a mus-

FIG 469—*TRANSECTION THROUGH THE BODY OF THE HUMAN UTERUS.*

g, blood vessels; *l,* lumen; *ll,* broad ligament; *lm,* longitudinal muscle; *m,* circular muscle (the fibers are mostly oblique); *s,* serous coat; *tp,* mucosa. Hematoxylin and eosin. ×2. (Sobotta.)

cular coat, and an outermost serous coat which is derived from the peritoneum and invests the body of the organ. The cervix uteri projects into the vaginal canal and the serous coat is there replaced by a reflection of the vaginal mucosa.

The *serous coat*, or *perimetrium*, of the uterus consists of mesothelium which rests upon a thin subepithelial layer of connective tissue. It presents no peculiarities.

The *muscular coat*, or *myometrium*, of the uterus consists of smooth muscle whose fibers are of large size (40 to 60 μ in length) and which are disposed in interlacing bundles. In the lower mammals these form quite regular layers—an outer longitudinal, a thick inner layer, most of whose fibers are circular, and an innermost, but less distinct, submucous portion containing oblique and longitudinal fibers. The outer longitudinal and circular layers are separated by a fibromuscular stratum containing a rich plexus of large blood vessels.

tion of the serous coat contains the larger vessels and nerves, which are distributed to the inner coats.

Blood Supply.—The arteries of the oviduct are derived from the uterine and ovarian vessels. The larger divisions find their way through the connective tissue of the serosa whence they send smaller branches inward to form a plexus between
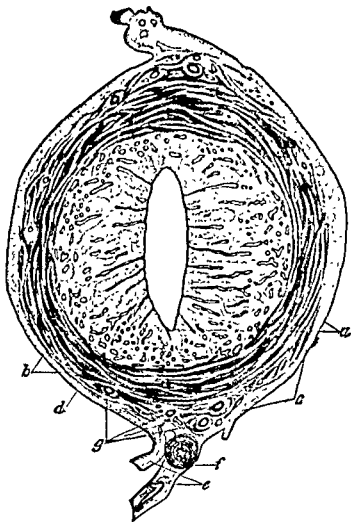
FIG 468 —TRANSECTION OF THE UTERUS OF AN APE.

a, mucosa; *b*, circular muscle; *c*, longitudinal muscle; *d*, serous coat; *e*, lateral ligament; *f*, wolffian tube; *g*, blood vessels ×4 (Sobotta)

the layers of the muscular wall and among the bundles of circular muscle fibers. From this plexus capillaries are distributed to the muscular coat, and to the mucous membrane in which they form a rich subepithelial capillary plexus. The veins follow a similar course, and like the arteries, form an extensive plexus in the muscular coat. The abundance of vessels in the muscular wall of the oviduct has led to the description of this coat as the vascular layer of the organ.

The *lymphatics* arise by anastomosing plexuses in the mucosa, from which

vessels pass to the serous coat and enter valved lymphatics by which the lymph is conveyed to the lymph nodes of the lumbar region.

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In the human uterus the arrangement of muscle fibers is much less regular, but follows a similar plan, though there is no distinct subdivision into layers. Nevertheless, careful examination reveals three indistinct strata which are intimately blended with one another. The outermost of these indistinct layers consists of irregularly disposed longitudinal fibers, the *stratum supravasculare.* This layer is in most parts very thin, and is best developed opposite the margin of the lateral ligament and in the cervix uteri. Within this is a broad layer of interlacing bundles of more or less circular fibers, which, from the slight obliquity of their course, frequently

FIG 470—FROM A TRANSECTION OF THE UTERINE MUCOSA.
×16. (Williams.)

cross each other at acute angles. Intermingled with these circular bundles are many large blood vessels, from which both the mucous and muscular coats are supplied. This broad middle layer is therefore known as the *stratum vasculare.* The inner portion of this second layer passes insensibly into a thin innermost *stratum submucosum,* which again contains many longitudinal fibers, and upon which the mucosa directly rests.

The *uterine mucosa,* or *endometrium,* is of considerable thickness (1 to 3 millimeters). It is clothed with epithelium, and its lamina propria contains numerous tubular glands.

The *epithelium* is of the ciliated columnar type, and consists of a single row of cells. Apparently not all of its cells are provided with cilia, areas of ciliated alternating with groups of nonciliated epithelium. The epithelial layer is continuous with the epithelium of the uterine glands; in the region of the external os uteri it is replaced by the stratified squamous epithelium of the vaginal mucosa.

Ofttimes, and especially in multiparae, the stratified squamous epithelium of the vagina is continued for some little distance within the canal of the cervix uteri; it never clothes more than the lower one-half to two-thirds of the cervical canal. The current resulting from the vibration of the intra-uterine cilia is directed toward the vagina.

The *lamina propria* of the mucosa consists of a peculiar embryonal type of connective tissue, similar to that of the uterine tubes, which contains very few
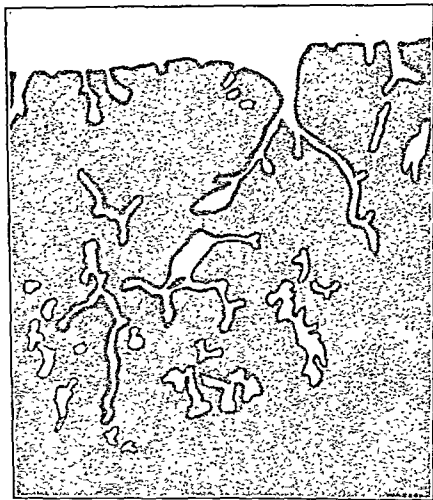
FIG. 471—FROM THE CERVIX UTERI OF A GIRL OF SIXTEEN YEARS, SHOWING THE CERVICAL GLANDS IN SECTION. ×102.

collagenous and no elastic fibers, but which is richly supplied, in fact is literally packed, with cellular elements. These cells are ovoid or fusiform in shape, and many of them are branched; their nuclei, also, are ovoid and somewhat vesicular. Many lymphocytes are found in the lamina propria, but these mostly occur in the vicinity of the lymphatics and smaller blood vessels with which the uterine mucosa is abundantly supplied. In the mucosa of the cervix uteri the development of the connective tissue appears to be more advanced, the cellular elements being relatively fewer; it also contains many fine fibers which appear to form a delicate net-

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The *blood vessels* of the uterus enter through the folds of the lateral ligament and find their way, through the subepithelial connective tissue of the serous coat and the muscular wall, to all portions of the organ. In the vascular layer of the muscular coat they form an extensive plexus from which branches are distributed to the musculature and to the mucosa, the branches to the latter penetrating nearly to the surface, where they form rich, subepithelial, capillary and venous plexuses. The uterine arteries, like those of the ovary, possess a peculiar, spirally tortuous course. The veins accompany the arteries, but are less tortuous.

The *lymphatics* of the uterus arise by anastomosing channels in the mucous and muscular coats. They form a vascular plexus in the serous coat and lead outward, through the lateral ligaments and pelvic connective tissue, to the lower lymph nodes of the lumbar region.

The *nerves* of the uterus are very numerous. They include both spinal and sympathetic fibers. *They enter the serous coat from the ganglionic pelvic plexus,* and are distributed to the vascular layer of the muscular coat. They there form a rich plexus, from which sympathetic motor fibers are distributed to the musculature and to the walls of the blood vessels.

The detailed distribution of nerves within the mucosa remains uncertain. Von Gawronsky [24] and Köstlin [25] describe sensory nerve fibrils which penetrate nearly to the surface and form a scanty subepithelial plexus, whence are derived fibrils which terminate between the epithelial cells.

Since the uterus is subject to extensive structural variations dependent upon its functional phase and condition, it becomes important to recognize the differential marks of the *menstruating* and of the *pregnant* uterus. Besides general histologic alterations in the wall, especially in the mucous and muscular layers, additional structures involved in the pregnant uterus are the *decidual cells* and *chorionic villi;* these are diagnostic of pregnancy. Only the histology of these structures will be here described, for a consideration of their embryologic significance and relationship reference must be made to a textbook of embryology.

The Menstruating Uterus

The appearance of the phenomena of menstruation is accompanied by decided alterations in the structure of the uterine mucosa. In spite of the difficulty of obtaining sufficiently fresh and well preserved material, certain changes which characterize the menstruating uterus are now definitely known. These chiefly consist in increased vascularity, hypertrophy of the elementary tissues of the mucosa, epithelial desquamation, and rupture of the blood vessels, with consequent hemorrhages. These changes are followed by a process of regression and later of regeneration, by which the uterine mucosa rapidly returns to its former condition.

The superficial layer (*stratum functionalis*) of the endometrium undergoes a definite series of changes during the menstrual cycle. These changes are under hormonal control. The *stratum basalis* of the endometrium only serves for repair

[24] Von Gawronsky, 1894
[25] Köstlin, 1894

work. At the external os uteri the lamina propria is continuous with the similar, though still more fibrous, layer of the vaginal mucosa.

The *uterine glands* are divisible into two types—those of the body of the organ, and those of its cervix. The former are, perhaps, to be regarded as tubular invaginations of the lining epithelium, whose function is one of epithelial regeneration rather than of glandular secretion. The tubules of the cervix uteri are true mucus-secreting glands.

The uterine glands proper, those of the body of the organ, are slightly branched or forked tubules which traverse the entire breadth of the mucosa, presenting a characteristic spiral or corkscrew course; their blind extremities are often bent or turned to one side, apparently from the proximity of the adjacent muscular coat. The glandular epithelium is of the columnar type and, like that of the free surface, is frequently provided with cilia, especially near the mouth of the gland. The epithelium rests directly upon the connective tissue of the lamina propria.

The *cervical glands* (*glandulae uterinae cervicales*) resemble those of the body of the organ in their tubular form and the columnar shape of their epithelium, but here the resemblance ceases. The cervical glands are much branched, and their tubules present frequent dilatations, some of which, apparently from occlusion of their outlet, attain a macroscopic size, and are then known as *nabothian follicles* (*ovula nabothi*); they are filled with a tenacious mucous secretion. The glandular epithelium near the crypt-like ducts is usually ciliated, like that of the surface. In the secret-

FIG. 472.—A GLAND OF THE HUMAN CERVIX UTERI IN LONGITUDINAL SECTION.

×90. (Williams.)

ing portions it consists of tall, clear, columnar cells which are in various stages of secretory activity, their product being a viscid glairy mucus, strings and granules of which are found within the lumen of the glands, as well as within the canal of the cervix uteri.

The *uterine cavity* is a relative term. In the virgin, the mucosa is considerably folded and its surfaces are almost in apposition, being only separated by a very limited amount of desquamated epithelium and cellular *débris*, to which, in the canal of the cervix uteri, the mucous secretion is added. During pregnancy, the development of the fetus within the uterine cavity distends its walls and so dilates the canal that it at last forms a sac of sufficient size to contain the fetus, which floats within the amniotic fluid inclosed by its membranes

FIG. 474.—VERTICAL SECTION OF UTERINE MUCOSA, ILLUSTRATING CONDITION ON EIGHTH DAY OF THE HUMAN MENSTRUAL CYCLE.

Note superficial compact zone. ×75 (Kurzrok.)
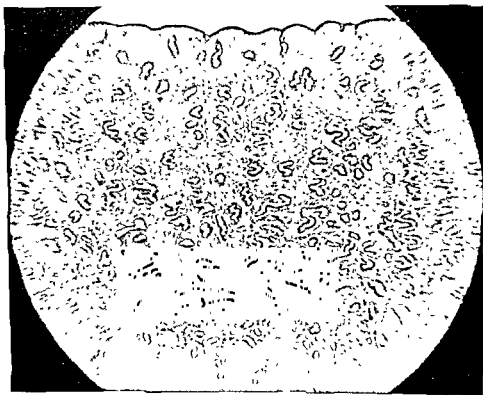
FIG. 475.—VERTICAL SECTION OF UTERINE MUCOSA AT FOURTEENTH DAY OF HUMAN MENSTRUAL CYCLE.

Note the tortuous condition of the glands. ×75. (Kurzrok.)

following the destruction of the superficial layer during the menstrual phase of the cycle. The cycle is divisible into the *menstrual*, *proliferative* and *secretory* phases. The stratum functionalis consists of an inner denser lamina (*compacta*) and an outer spongy lamina (*spongiosa*). At the beginning of the *menstrual phase* the blood vessels of the mucosa become greatly engorged and finally rupture with hemorrhage into the interstitial tissue and subsequently into the uterine cavity. The entire stratum functionalis progressively desquamates leaving the stratum basalis
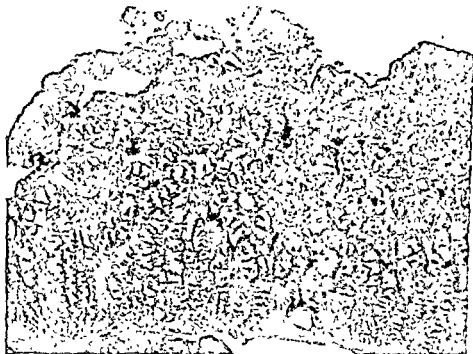
FIG. 473—VERTICAL SECTION OF UTERINE MUCOSA, SHOWING INITIAL PHASE OF THE HUMAN MENSTRUAL CYCLE (BEGINNING OF BLEEDING).

Note subepithelial hemorrhage and desquamation. ×75. (After Kurzrok, *Endocrines in Obstetrics and Gynecology*, Williams and Wilkins, Baltimore, 1937.)

exposed by the end of the fourth day (Fig. 473). In the succeeding *proliferative phase* new epithelium arises from the glands of the basalis. In this phase the mucosa has a thickness of about 2 mm. as compared with the preceding phase when it has a thickness of only about 0.5 mm. The glands are now long and straight tubules with an increasing number of mitotic figures in the lining cells but with no secretion (Fig. 474). The proliferative phase terminates on about the tenth day, the onset of ovulation, and under the influence of the follicular hormone, *estrone*.

The *secretory phase* lasts from ovulation to menstruation—about fourteen days. The glands become progressively more tortuous (Figs. 475 and 476). The cells become wider and taller. Glycogen appears in the cells. Meanwhile, the thin-wall blood vessels and capillaries dilate. Lymphocytes appear in the stroma and the epithelium assumes an endothelioid character. The glands produce an abundant

together with the atrophied remains of the uterine glands, and a superficial *compact layer* in which the vascular channels, except for the thin-walled venous spaces, are smaller and the connective tissue cells more closely packed.

Many of the connective tissue cells attain a large size and their nuclei are frequently multiple, occasionally polymorphous. Giant cells are thus produced in the compact layer of the mucosa of the gravid uterus; they are highly characteristic of this tissue and are known as decidual cells. Though it is frequently asserted that similar cells occur in the decidual menstrualis, this is denied by Minot (1903), who states that in a considerable number of menstrual decidua examined, no such cells were ever found.
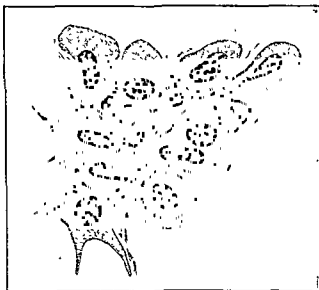
FIG. 477.—A GROUP OF DECIDUAL CELLS FROM THE HUMAN UTERUS DURING THE EARLY STAGES OF PREGNANCY.

One of the cells contains two nuclei and a number of fat vacuoles. Three nuclei of the connective tissue stroma are also shown. ×750.

The superficial epithelium is soon desquamated and the lamina propria comes into contact with the fetal chorion. The glandular epithelium is also partially degenerated, often becoming flattened and of irregular shape. It is frequently desquamated into the glandular lumen. This lumen is thus reduced to a narrow crevice, which is so elongated during the dilatation of the uterine wall that the axis of the glandular remnant becomes nearly parallel to the surface of the decidua.

The decidual membrane which is thus formed is divisible into three portions, according to its relation to the tissues of the embryo: (1) that portion upon which the developing ovum directly rests, which is known as the *decidua serotina* or *decidua basalis* but later forms the *placenta uterina* or maternal portion of the placenta; (2) at the margins of the implanted ovum the decidual tissues close up over the ovum which is thus surrounded by the so-called *decidua reflexa* or *decidua capsularis*, which, after the early months of pregnancy, is gradually obliterated by the increasing growth of the fetus, and is finally replaced, its functions being progressively usurped by the newly formed placental tissues; (3) all the remaining portions of the decidual mucosa, those which line the greater part of the uterine cavity, collectively form the *decidua vera*, with whose surface, in the later months of pregnancy, the fetal chorion is intimate in relation.

The mucosa of the cervix uteri meanwhile becomes greatly hypertrophied and its glands much enlarged. This portion of the uterine mucosa does not, however, enter into

glairy secretion. This phase ends with the onset of menstruation. While menstruation is commonly regarded as the beginning of the cycle, it is more properly interpreted as terminating a preceding menstrual cycle. For further details reference

FIG. 476.—HUMAN UTERINE MUCOSA ON TWENTY-EIGHTH DAY OF MENSTRUAL CYCLE. Glands very tortuous, stroma scanty. ×75. (Kurzrok.)

should be made to an article by G. W. Bartelmez and Carey Culbertson on "Histological Studies on the Menstruating Mucous Membrane of the Human Uterus" (Contributions to Embryology, vol. 24, Carnegie Institution of Washington, 1933).

The Gravid Uterus

In the event of conception the uterine changes are more pronounced than during menstruation. These alterations include the same processes of hypertrophy and thickening as occur in the decidua menstrualis; they involve the musculature as well as the mucosa but are not followed by regressive changes—hemorrhage, desquamation, etc.—until parturition occurs.

The muscular wall undergoes an enormous increase both in the number and size of its fibers. The relatively short (30 to 60 μ) smooth muscle fibers of the uterine wall gradually increase in size to as much as eleven times their former length and two to five times their breadth (Kölliker). The connective tissue of the muscular coat also increases in volume and becomes more distinctly fibrous. After parturition, fat droplets appear within the muscle cells, and the muscular wall by gradual atrophy returns to its former condition.

In the mucosa the formation of a decidual membrane goes forward in a manner similar to the development of the decidua menstrualis, but the process is exaggerated. The lamina propria soon becomes divisible into two distinct, though not sharply defined, layers, a deeper *cavernous portion* which is permeated by broad vascular channels

Langhans with their large ovoid nuclei, and a core of connective tissue of a delicate embryonic type, in which are the *fetal* blood vessels. Even the smallest villi contain capillary loops of broad caliber, which are supplied by fetal arteries, derived from the umbilical arteries, which distribute their branches throughout the chorionic connective tissue The fetal veins accompany the arteries.

FIG 479—CHORIONIC VILLUS AT VARIOUS STAGES OF DEVELOPMENT.

A, chorionic villus at third week, *B*, at fourth month; *C*, at term. (Williams.) ×225.

The Vagina

The vagina is a fibromuscular sheath whose wall is divisible into three coats—mucous, muscular and fibrous

Mucous Membrane.—The mucous membrane is clothed with a layer of stratified squamous epithelium, and is thrown into numerous folds or rugae. The epithelium rests upon a fibrous basement membrane. The lamina propria is formed by a close-meshed areolar tissue which, in its deeper and looser portion, is permeated by vascular channels of considerable size. This deep vascular layer is frequently described as a submucosa; it rests directly upon the muscular wall. The surface of the mucosa presents numerous conical papillae which project well into the epithelial layer.

Musculature.—The musculature of the vagina contains smooth or involuntary fibers, and is divisible into an inner circular and an outer longitudinal layer. The muscle fibers are long and slender. Considerable connective tissue is distributed among the muscle bundles. The latter are arranged in more or less parallel layers which are united by the delicate bands of connective tissue.

Outer Fibrous Coat.—The outer fibrous coat consists of dense areolar tissue which is well supplied with elastic fibers. It loosely unites the vaginal wall to the surrounding tissues. In this coat is a plexus of blood vessels and lymphatics, from which branches pass to the muscular coat, and to the mucosa, in which they form an abundant plexus. An extensive nerve plexus, including spinal and sympathetic fibers, among which are many small ganglia, is also found in the fibrous coat; it distributes motor branches to the muscular wall and to the blood vessels, and sensory fibers to the mucosa, in which they end in relation with the cells of the lining epithelium.

the formation of the decidua vera; the changes occurring in its tissues, though similar, are much less pronounced.

Chorionic Villi.—These innumerable processes form the greater portion of the placental tissues. They vary in size from the broad stems to the very slender terminal branches of the floating villi. They consist of a core of mesoderm covered with a variable layer of ectoderm. In the early condition of the placenta (fourth or fifth month of pregnancy) the villi are clothed with a double epithelial layer, of which the

FIG. 478.—CHORIONIC VILLI FROM THE HUMAN PLACENTA AT FULL TERM.
Hematein and eosin. Photo. ×114.

superficial takes the form of a syncytium (plasmoditrophoblast), while the deeper consists of a cellular layer, the *cells of Langhans* (cytotrophoblast). At later periods (seventh month to full term) the syncytium is found to have undergone a peculiar alteration, having become *much thinner, and having even completely disappeared from considerable portions of the villi*, it being replaced by canalized fibrin. At other points the syncytical cytoplasm is much thickened and the nuclei appear to be bunched or grouped within the thickened portions; these areas are known as *cell-knots* or *proliferation islands*. Here and there the degenerated cell-knots have been replaced by canalized fibrin. Wherever the main stems are inserted into the decidua the epithelium which formerly covered their tips appears to have also degenerated into a peculiar hyaline border zone. Towards the end of pregnancy the cytotrophoblast becomes converted into plasmoditrophoblast.

Within its syncytium the substance of the villus consists of the superficial cells of

an isolated blind duct, usually in the wall of the uterus and vagina, is known as the canal of Gartner. It is the vestige of the lower portion of the fetal wolffian duct.

Appendix fimbriae

Fimbria ovarica

Müllerian duct

Pronephric tubule

Epoophoron

Paroophoron

Mullerian duct

Uterus

Canal of Gartner
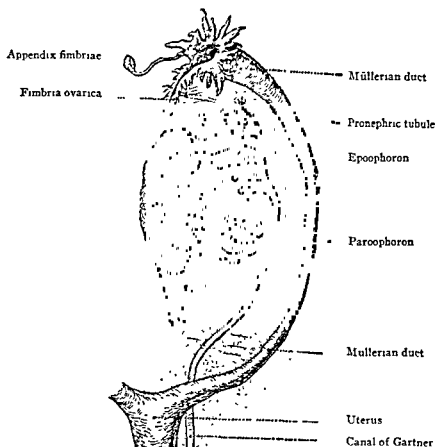
FIG. 481.—DIAGRAMMATIC REPRESENTATION OF THE VESTIGIAL STRUCTURES OF THE GENITAL SYSTEM OF THE FEMALE HUMAN EMBRYO. (Kollmann.)

THE EXTERNAL GENITALS

Vestibule.—The vestibule is supplied with a mucosa which offers a gradual transition from the vagina, on the one hand, to the skin on the other. Its stratified squamous epithelium becomes in this way gradually more and more like that of the skin, eleidin granules first, and keratin later appearing on the outer surface of the labia minora. The epithelium of the labia majora is identical with that of the skin.

Labia Minora.—The labia minora or nymphae form the lateral walls of the vestibule and consists of a fold of the mucosa which is provided with exceptionally tall papillae. Small sebaceous glands open directly upon the surface of the stratified squamous epithelium. There are no hair follicles in relation with these glands, and the labia minora contain no adipose tissue. They are richly supplied with blood vessels, and with sensory nerve endings.

Labia Majora.—The labia majora are formed by similar folds whose inner surface resembles the adjacent portion of the labia minora, but whose outer surface is cutaneous and is supplied with sebaceous and sudoriparous glands and

The vaginal mucosa is reflected upon the outer wall of the cervix uteri, and at or near the external os it is continuous with the mucosa of the uterine cavity. Though occasional glands have been found in the vaginal mucous membrane, lined either by mucus-secreting or by ciliated cells, these glands would seem to be prop-
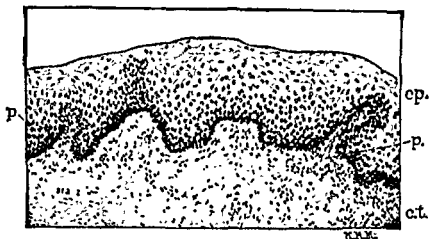
Fig. 480.—VAGINAL MUCOSA. ×90

ep., epithelium; *p.*, papilla; *c.t.*, connective tissue. (Williams.)

erly considered as anomalies, since they are usually absent, the mucoid secretions of the vaginal canal being chiefly provided by the abundant supply of mucus from the cervical glands of the uterus. The vaginal mucosa is continuous below with that of the vestibule.

The Vestigial Structures

The vestigial structures associated with the female reproductive system include the vesicular appendage (hydatid of Morgagni), the epoophoron, and the paroophoron. The same general statements made concerning the male vestigial structures hold likewise for those of the female.

Vesicular Appendage.—The vesicular appendage is attached to the fimbriated end of the oviduct, its stalk being continuous with the collecting duct of the epoophoron. It is a globular pedunculated structure of small size (3 to 6 millimeters diameter); it is lined with cuboidal epithelium, and may contain fluid. It represents the atrophic end of the degenerated wolffian duct. There are besides a variable number of smaller accessory vesicular appendages attached to the broad ligament.

Epoophoron.—The epoophoron (parovarium; organ of Rosenmüller) lies between the layers of the broad ligament in the triangular area between the ovary and the ampulla of the oviduct. It consists of a variable number of tubules (eighteen to twenty), the homologues of the ductuli efferentes of the male. These tubules may be blind at only one or at both ends; they may be lined with ciliated columnar epithelium, or their lumina may become obliterated. Those blind only at one end connect with a longitudinal duct, a variable remnant of the wolffian duct.

Paroophoron.—The paroophoron—homologue of the male paradidymis—is a more mesial collection of similar tubules of like structure and genetic significance. It is said to be present only in infants. The further extension mesially of the longitudinal duct, either in continuation with the collecting duct of the epoophoron or paroophoron, or as

ance of microscopical sections of the gland, varies according to the stage of development and the condition of activity of the organ.

The Active Gland.—During lactation the glandular alveoli are so numerous as to form by far the most prominent portion of the gland. Each lobule consists
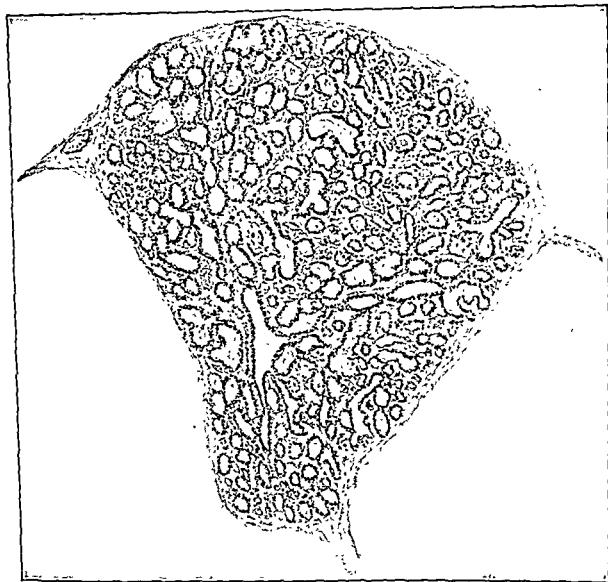
FIG. 482—HUMAN MAMMARY GLAND AT LATE STAGE OF PREGNANCY.

The section shows one large lobar duct (near lower left border), several interlobular branches, and many alveoli filled with secretion. ×60.

of a cluster of saccular alveoli which open by short alveolar (intralobular) ducts into the interlobular ducts of the connective tissue which invests the lobules of the gland. The alveoli are closely packed within the lobule.

The actively secreting alveoli are lined with cuboidal or low columnar cells which vary much in height even within the same alveolus, and are often considerably flattened. Fat droplets accumulate within the distal portion of their cytoplasm 'The droplets increase, in size as well as in number, until they finally occupy

with numerous hair follicles. The subepithelial areolar tissue is very dense and its deeper portion contains much fat.

Clitoris.—The clitoris consists of a mass of erectile tissue, homologous with the corpora cavernosa and glans penis of the male; it is covered by a fold of the mucosa. It is well supplied with nerves, which terminate in tactile corpuscles, end-bulbs, and genital corpuscles. In this vicinity also, as well as in the region of the labia, pacinian corpuscles are occasionally found.

Hymen.—The hymen is a thin membrane formed by a reduplication of the vestibular mucosa. Its inner surface is similar to that of the vagina. Its outer surface is like that of the labia minora.

Glandulae Vestibulares Minores.—The glandulae vestibulares minores are a group of small mucus-secreting glands, similar in structure to the urethral glands of Littré in the male, which occur in the vestibular mucosa in the vicinity of the meatus urethrae.

Glandulae Vestibulares Majores.—The glandulae vestibulares majores (glands of Bartholin) form a pair of tubulo-alveolar mucus-secreting glands which open by a narrow duct into the groove between the hymen and labium minus. The tubular alveoli are lined with columnar mucus-secreting cells. The ducts are clothed with columnar epithelium, which, as they approach their termination, becomes double-rowed, and finally changes to a stratified squamous epithelium similar to that of the surface upon which they open. These ducts frequently present saccular dilatations.

THE MAMMARY GLANDS

From a strictly histogenetic standpoint the mammary glands should be considered as appendages of the skin, and as such should more properly have been considered in the chapter devoted to that subject. Yet these glands are so closely related to the reproductive functions, attaining their full development only in the lactating female, that it seems equally proper to consider them at this time as accessory reproductive organs.

The mammary glands may be regarded as modified sweat glands. Though producing a fatty secretion they show no resemblance to sebaceous glands. The mammae undergo the same slight but progressive development in both sexes until the time of puberty when they suffer regressive changes in the male, persisting thereafter only in rudimentary condition. In the female they continue to grow, but become functionally active only in the event of pregnancy. Upon the hemispherical *corpus mammae* can be distinguished the central raised *nipple* or *mammilla*, and the surrounding roughened and pigmented circular area, the *areola*.

Each mammary gland consists of fifteen to twenty lobes, each of which is of itself a branched saccular gland whose *lactiferous duct* opens on the surface of the nipple near its apex. The main lactiferous or lobar ducts subdivide in an arborescent manner into many interlobular ducts, about which are clustered the groups of secreting alveoli, each group forming one of the many lobules included in a lobe of the gland. The structure of the lobule, as well as the general appear-

demonstrable. The thin lamina propria is, however, richly supplied with blood capillaries, lymphatic vessels and nerve fibers.

The ducts of the mammary gland are lined with either a single or double row of low columnar cells. They possess a relatively broad lumen. Their membrana propria is supported by a thin connective tissue wall, containing both circular and longitudinal elastic fibers but no muscle. The elastic fibers of the smaller ducts are poorly developed, but in suitable specimens the longitudinal fibers are readily seen even in very small branches. Beyond the lactiferous sinus the duct epithelium changes to a stratified squamous variety which is continuous with that of the cutaneous surface of the nipple.

The glandular lobules are firmly united by strong septa derived from the dense areolar tissue in which they are embedded. In the deeper parts of the gland occasional lobules of fat are found in this tissue. Within the nipple and beneath the adjacent portions of the areola, smooth muscle fibers are also found. These are arranged in circular bundles at the base of the nipple, with longitudinal fibers within its substance which, at the base of the mammilla, diverge in radiating bundles into the subcutaneous tissue of the areolar zone. Contraction of these fibers elevates and hardens the nipple, thus stimulating the action of the erectile tissues.

FIG. 484.—PORTION OF ACTIVE ALVEOLUS OF MAMMARY GLAND OF RABBIT 25 DAYS AFTER BEGINNING OF PREGNANCY.

The lumen contains a vacuolated secretion, its more solid portions representing apical cytoplasm in process of separation from the secreting cells. Below the alveolus, at the right, appears a myoepithelial cell. ×1109 (Schil.)

Elastic fibers are more abundant than was formerly recognized in the walls of the alveoli and in the interalveolar connective tissue, frequently in intimate association with smooth muscle cells. Such "elastico-muscular apparatus"[28] is well developed in the peripheral portion of the glands, in the subpapillary layer of the skin, and especially in the vicinity of the nipple. The elastic fibers, which are superficially distributed, appear embedded at their deeper ends in the muscle fibers. This peculiar arrangement of elastic fibers in relation to smooth muscle probably aids in the expulsion of the secretion.

Embedded in the subcutaneous tissue of the areola are also a number of small accessory lactiferous glands known as the *glands of Montgomery (areolar glands of Duval)*. The nipple and areola contain also abundant sebaceous glands, and sweat glands are present in the periphery of the areola.

The Resting Gland.—With the cessation of lactation the glandular alveoli undergo a rapid atrophy, and are replaced by connective tissue derived from the interlobular stroma. The ducts contract and the epithelium piles up to form a two-rowed, or even thicker, layer. The alveoli are reduced to mere buds from the terminal ducts, and their lumen is almost obliterated; their epithelium is similarly massed into a double layer of small cells. The lobules are reduced in size and con-

[28] Liporovsky, 1914.

the greater part of the distal end of the cell and are separated from each other by only a narrow interval of albuminous cytoplasm. Finally the fat droplets are discharged into the broad lumen of the alveolus, where they apparently still retain a thin albuminous envelope which prevents their cohesion and consequent fusion, and thus permits their suspension in the albuminous, fluid portion of the milk. The milk may include also cytoplasmic and nuclear débris. The functional cycle of the mammary glands of the rabbit has been investigated in great detail by Schil.[26]

The spherical nuclei of the secreting cells during this process are crowded
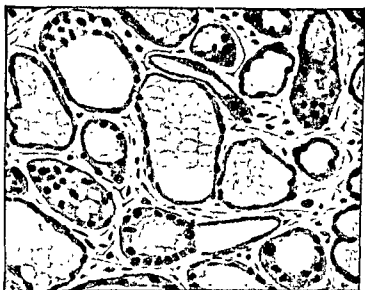
FIG. 483.—ACTIVE MAMMARY GLAND OF RABBIT (TWENTY-TWO DAYS AFTER FECUNDATION). The alveoli are filled with milk containing fat droplets. ×416 (Schil.)

to the base of the cell, and after the discharge of the secretion the shrunken but nucleated cell remnants remain *in situ;* after a period of rest the cells apparently resume their secretory function. It appears probable · that each cell in its life history may repeatedly pass through the cycle of secretory changes, though the exact number of such cycles which an individual cell may present obviously does not admit of demonstration. They are of the merocrine or apocrine type of gland.

As a rule, the active epithelium consists of a single row of cells, though here and there they appear as if piled upon one another to form a double layer. During pregnancy many of these cells may be seen in mitosis. The actively secreting cells contain basal (ergastoplasmic) filaments. These filaments break up into granules from which minute fat spherules develop.[27] The epithelium rests upon a reticular or homogeneous basement membrane, within which are occasional *basket cells.* These have been interpreted as smooth muscle cells, similar to those of the secretory portions of the sweat glands. The alveoli of the active gland are so closely packed that a connective tissue lamina propria is no more than scarcely

26 Schil, 1912.
27 Hoven, 1911.

comes to the conclusion that the colostrum corpuscles are in part epithelial cells of the acini and galactophoric canals.

Lewis and Wells [31] interpret the function of colostrum in terms of the chief source of supply of protective antibodies associated with euglobulin, which latter' is said to be lacking in the blood of the newly born. Activity of the mammary gland appears to be directly under the influence of the placenta. During pregnancy new acini begin to be differentiated about the third month. Several days after parturition milk is secreted. Philips [32] has been able to stimulate colostrum secretion in non-pregnant middle-aged women by implantation of placental tissue of the third month of pregnancy into the abdominal wall.

The *blood vessels* of the mammary gland are specially abundant They form rich capillary plexuses about the walls of the active alveoli Many of the venules coming from these plexuses converge toward the areola, where they form an incomplete venous circle (*circulus venosus of Haller*) from which the efferent veins take their origin.

The *lymphatics* of the mammary gland are also numerous. They take origin from broad channels among the alveoli and enter a rich plexus about the interlobular ducts. From here several vessels pass to the lymph nodes of the axilla.

The *nerves* of the mammary gland include both spinal (sensory) and sympathetic fibers. The latter are distributed to the vascular walls, to the smooth muscle of the areola and nipple and to the alveolar epithelium The sensory fibers supply the connective tissue of the nipple and areola where they occasionally terminate in tactile and pacinian corpuscles. Among the secreting alveoli the nerve fibers form a epilemmal plexus beneath the membrana propria, from which fibrils penetrate between the epithelial cells, upon which they end in minute granular varicosities.[33]

FIG 486.—FROM A SECTION OF THE HUMAN MAMMARY GLAND IN THE RESTING CONDITION

a, remnants of the glandular alveoli, *b*, duct; *c*, connective tissue. Certain regions of the fibro-elastic stroma usually contain variable amounts of adipose tissue. Hematein and eosin. ×10

Milk.—Milk, secreted by the active mammary gland, consists of an emulsion, in which fat droplets, varying in size from two to twenty microns or more, are suspended in a watery albuminous fluid Water constitutes about 86 per cent of the secretion. The protein constituent (3 per cent), which is largely nuclein, is derived in part from degenerating nuclei. Milk contains also a small amount of

[31] Lewis and Wells, 1922.
[32] Philips, 1924
[33] Arnstein, 1895

sist only of a few shrunken alveoli clustered about the termination of an interlobular duct. The lumen of the alveoli, if any, contains no secretion, and that of the ducts, except for a little granular albuminous material and an occasional leukocyte, is empty.

The connective tissue stroma is much increased in volume, and in places shows a marked infiltration with fat. The alveolar tissue of the mammary gland at all times contains wandering leukocytes, and many granule cells, both acidophil and basophil in character.

With the appearance of pregnancy the gland promptly reënters a state of activity. Its alveoli multiply; its connective tissue becomes relatively diminished in volume; its lobules are reformed and their alveoli finally begin secretion. Secretion is heralded by the formation of a granulofatty colostrum, a rather serous fluid in which are suspended large numbers of *colostrum corpuscles*, large spheroidal cells, resembling leukocytes in their general form and in the character of their nuclei, but which possess a broad rim of cytoplasm often containing numbers of fat globules of varying size. Their cytoplasm has also been shown to contain neutrophil granules of Ehrlich similar to those of the polymorphonuclear leukocytes.[29]

FIG. 485.—MODEL OF A RECONSTRUCTION OF AN INTRALOBULAR DUCT AND ITS ALVEOLI FROM THE ACTIVE MAMMARY GLAND OF A WOMAN.
×200. (Maziarski.)

Colostrum discharge precedes and follows the period of lactation for a few days; a similar secretion appears also in both sexes for several days after birth when it is commonly known as "witch's milk."

The origin of the colostrum corpuscles is still somewhat in doubt, though modern technic has gradually discredited the theory of their origin from desquamated remnants of the alveolar epithelium. They are more probably enlarged leukocytes which have wandered through the alveolar wall and have thus found their way into the lumen, where they take on a phagocytic activity and continue their growth. The following facts may be mentioned in support of this theory: (a) leukocytes can be readily found between the cells of the alveolar epithelium as well as in the lumina of the saccules; (b) the colostrum corpuscles examined in a fresh condition on a warmed slide have been repeatedly shown to possess the property of ameboid motion; (c) the colostrum corpuscles when stained, present the same granular and nongranular varieties as do the leukocytes of the blood; (d) finally, the colostrum corpuscles have been shown to undergo mitotic cell division, a phenomenon which we should hardly expect to find in degenerated and desquamated epithelial cell remnants. However, Gregoire[30] in his investigation

29 Michaelis, 1898.
30 Gregoire, 1931.

CHAPTER XVI

THE DUCTLESS GLANDS, ENDOCRINE GLANDS
(Organs of Internal Secretion)

Under this heading it will be convenient to consider the suprarenal, thyroid, parathyroid, thymus, carotid, and coccygeal glands, the paraganglia, hypophysis cerebri and the epiphysis cerebri. This group of organs properly includes also the pancreatic islets, the interstitial cells of the testis and the ovary, the corpora lutea, the duodenal mucosa, the gastric mucosa and the liver, already described.

SUPRARENAL GLANDS

The suprarenal glands (bodies or capsules, also called *adrenals*) are two flattened irregular glandular masses situated close to the cranial extremity of each kidney, but without organic or genetic relationship with the renal system. Each weighs about one-seventh of an ounce. On section the adrenal is seen to be readily divisible into a bright yellow or brownish-yellow *cortex* and a more vascular, and hence darker and somewhat reddish, *medulla*, whose central portion transmits several large veins which make their exit from an indentation in the anterior surface of the organ, known as the *hilus*.

Histologic Structure.—The organ is inclosed by a connective tissue capsule of considerable thickness. From the inner surface of the capsule delicate fibrous trabeculae pass inward and subdivide the epithelial parenchyma of the organ into cell groups and columns, which vary in their appearance according to the distribution of the connective tissue trabeculae. The suprarenal parenchyma is exceptionally prone to postmortem changes. In the medulla the connective tissue presents an irregular areolar arrangement; the more regular, though varying form of the areolae in the cortex, subdivides this portion of the organ into three more or less distinct layers, which were first described by Arnold[1] as the *zona glomerulosa, zona fasciculata*, and *zona reticularis*.

In the zona glomerulosa the connective tissue trabeculae subdivide the epithelium into spheroidal groups of cells, many of which are continuous with the cell columns of the adjacent zona fasciculata. The glomerulate layer is relatively thin and lies close beneath the capsule.

The stroma of the zona fasciculata is continued inward from the glomerulosa,

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[1] Arnold, 1866.

sugar (5 per cent) and a trace of salt. Each fat droplet is presumably invested with a thin coat of casein, derived from the cytoplasm of the secreting epithelium. Occasionally leukocytes occur in the milk, but never in large numbers, and like the similar colostrum corpuscles, they are mostly confined to the earlier periods of lactation.

Recent experimental analysis of the mechanism of lactation indicates that growth of the ducts is dependent upon the ovarian (*follicular*) hormone *theelin* (*estrone*), growth of the acini upon the ovarian hormone *corporin* and secretory activity upon a lactogenic hormone (*galactin, prolactin*) of the pars distalis of the hypophysis cerebri. Reference should be made to Allen's *Sex and Internal Secretions,* Williams and Wilkins, 1939, and to Kurzrok's *The Endocrines in Obstetrics and Gynecology,* Williams and Wilkins, 1937.

columns. In man it passes almost insensibly into the medulla; in many animals—
e.g., the dog, cat, and pig—there is a sharp demarcation between the zona reticu-
laris and the medulla, produced by a thin membranous layer of connective tissue
which apparently results from the fusion of the central ends of the fibrous bands
in the cortical stroma. Such a membranous septum is usually wanting in the human
adrenal.

The connective tissue stroma of the suprarenal consists of a delicate vascular
network, which in the cortex contains very few if any elastic fibers. This connective
tissue is, in large part, at least, a reticular tissue. The capsule consists of dense
bundles of collagenous fibrous tissue among which are many elastic fibers. The
stroma of the medulla is also richly supplied with elastic tissue.

The *epithelium of the zona glomerulosa* is arranged in spheroidal groups or in
hooked or slightly coiled columns which are continuous with the straight columns
of the fascicular zone. The cells of the zona glomerulosa are closely packed within
the connective tissue meshes and the cell outlines are very indistinct. Wherever
their outlines can be readily distinguished the cells are seen to be of columnar
shape and are arranged in slender columns whose cells are often grouped about
an indistinct central lumen. The cytoplasm of the cells of this zone is finely granu-
lar and stains readily with acid dyes. Occasional minute fat droplets appear in
the innermost cells of the group, but these are never so abundant as in the more
internal portions of the cortex. The nuclei in this zone are spheroidal in shape
and rich in chromatin; they present frequent mitoses, but these are more abundant
in early life than in the adult.

The *cells of the zona fasciculata* are highly characteristic. They are arranged
in long straight columns which extend from the zona glomerulosa inward to the
zona reticularis. The cells are columnar or polyhedral in shape; many of them
contain minute fatty droplets in great abundance. This fat is readily blackened by
osmic acid. Arnold (1902), by extraction with ether, obtained crystals of palmitin
and stearin from the suprarenal gland Plecnik,[2] however, considers that the supra-
renal fat differs in its ultimate chemical properties from the other fat of the
body. Each columnar group consists of cells which are, as a rule, in approxi-
mately the same stage of fatty metamorphosis, and the cell columns of this zone
may be divided into those which are distinctly acidophil and those which are
distinctly fatty, though between these extremes there are many intermediate stages.

The acidophil cells are ovoid or polyhedral elements which possess one or two
highly chromatic spheroidal nuclei and a finely granular cytoplasm. On careful
examination with high magnification, extremely minute fat droplets may often
be demonstrated even in the most characteristic of these cells; with lower mag-
nification these are frequently invisible.

The fatty cells possess a spheroidal nucleus which is usually vesicular in char-
acter; occasionally it is highly chromatic. Frequently the apparent chromatolysis
seems to progress in exact ratio to the accumulation of fat; those cells in which

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[2] Plecnik, 1902

but is so drawn out as to form elongated areolae, inclosing cell columns of considerable length, which are disposed in a radial manner. This is the broadest of the three cortical zones and is interposed between the glomerulosa and reticularis.
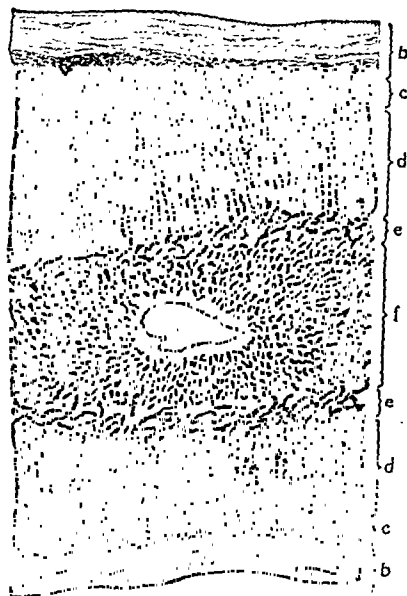
FIG. 487.—DRAWING OF SECTION OF CHILD'S SUPRARENAL

a, central vein, *b*, capsule, *c*, zona glomerulosa; *d*, zona fasciculata; *e*, zona reticularis; *f*, medulla

At the inner border of the zona fasciculata the connective tissue bundles pass insensibly from the regular columnar arrangement of this layer into a reticular maze. The resulting cell groups are of very irregular form and compose the innermost cortical layer, the zona reticularis. This layer is the thinnest and least distinct of the three zones of the cortex. It can often be more readily distinguished by the highly pigmented condition of its cells, than by the mere form of its cell

young persons, but is, as a rule, present after the twentieth year of life.[3] In the suprarenal of the mouse, and probably of other mammals, many of these cells can be seen in process of amitotic division. In young individuals (mouse) the zona reticularis is equally developed in both sexes. In the female it subsequently increases gradually in volume to the time of puberty; but in the male it disappears prior to sexual maturity, except for a few degenerate cells. In old females also the zona reticularis disappears almost entirely, the suprarenal consequently assuming essentially the same structure as in the male. Castration of the male restores the zona reticularis to the volume characteristic of the male infantile condition.[4] The various morphological types of cells in the cortex may be regarded as different stages in the life history of the same cell. It is reported that these gland cells may be derived in the adult suprarenal cortex from certain indifferent cells formed in the capsule.[5]

The suprarenal glands are significantly larger in the female than in the male sex, in consequence of a greater amount of cortex. "The cortico-medullary ratio averages 12.4 to 1 in the white males, 20 4 to 1 in white females, 8.3 to 1 in negro males and 14.2 to 1 in negro females."[6]

The *epithelial cells of the medulla* are ovoid elements with one or two spherical nuclei, which in many cases possess a vesicular character; in other cells they consist of a dense, almost solid, mass of chromatin. The shape of the cell groups in the medulla varies greatly; usually they form small spheroidal masses or short columns. The cells are frequently arranged in a more or less tubular form but without a distinct lumen. Frequently they surround a minute capillary vessel. The medullary cells presumably pour their secretion into the blood vessels, whose broad sinusoidal capillaries permeate the delicate connective tissue bands which inclose the cell groups. Felicine[7] claims to have demonstrated the presence of minute intra- and intercellular secretory canaliculi which open directly or indirectly through broader *lacunae*, into the blood vessels.

The cell groups of the medulla, like those of the cortex, are divisible into the acidophil and the fatty types; the former are the more abundant, but the fatty metamorphosis is scarcely ever so advanced as in the cortex. There is, however, great variation in the size of the medullary cells. The larger ovoid elements form the typical groups; between these groups are narrow cell columns consisting of much smaller and less highly acidophil cells, which are arranged in slender columns and scattered irregular masses.

The striking feature of the medullary cells is their granular content. These *chromaffin granules* have a special affinity for chromic acid and its salts, and stain a light brown or yellow. Their staining capacity in chromium solutions is due to the presence of *adrenalin*.[8] The granules are very readily soluble in acids.

[3] Maass, 1889
[4] Masui and Tamura, 1925.
[5] Zwemer, Wotton and Norkus, 1938.
[6] Swinyard, 1940.
[7] Felicine, 1904
[8] Kingsbury, 1911.

the fatty metamorphosis is more advanced present the more typically vesicular nucleus. With the progress of the fatty metamorphosis the cell outlines are again lost and the granular acidophil cytoplasm gradually replaced. The presence of fat in the broad zona fasciculata is partially responsible for the bright yellow color of the cortex of the organ.
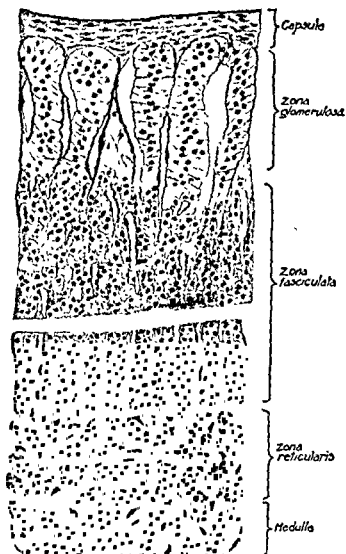
FIG. 488—MORE HIGHLY MAGNIFIED SKETCH OF SMALL PORTION OF PRECEDING FIGURE.

The *cells of the zona reticularis* are similar to those of the zona fasciculata, though the fatty metamorphosis is less pronounced. In one particular, however, the cells of this layer are remarkable. They contain an abundance of a peculiar *brownish-yellow pigment* which occurs both in the form of coarse granules and as a diffuse coloration of the cytoplasm. The spherical nuclei, highly chromatic or only slightly vesicular in character, are not invaded by the pigmentation. The volume of pigment varies greatly in different individuals; it is usually absent in

tomosis, through the medulla to the central veins. The venules of the cortex possess no walls other than their endothelium. The lining of the cortical capillaries and venules constitutes part of the reticulo-endothelial system of the Aschoff.

The *medullary arteries* are also derived from the capsular plexus. They penetrate the cortex, and at the border of the medulla abruptly terminate in a plexus of capillary vessels which lie in the connective tissue stroma and come into intimate relation with the medullary cells. These vessels possess extremely thin walls, their endothelium often being in direct contact with the adjacent epithelium, whose cells frequently impinge upon the lumen of the capillary vessel. The capillary plexus pervades the entire medulla, its vessels being here and there collected into small venules which unite to form the central veins (see Fig. 490). These form
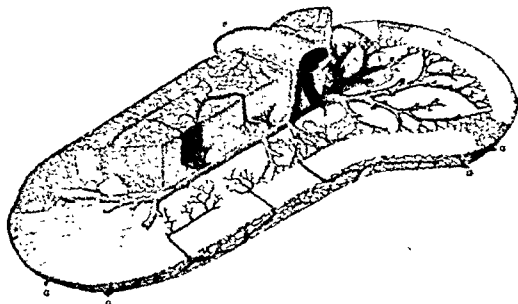
FIG 490—RECONSTRUCTION OF A DOG'S SUPRARENAL.
a, arteries; *v*, vein. ×25. (Flint)

two, or sometimes four, main stems (Flint) which make their exit at the hilus and enter the lumbar or renal vein, or, on the right side, enter the inferior vena cava.

All of the efferent veins of the adrenal are characterized by a peculiar distribution of their smooth muscle fibers, which occur in considerable abundance, but are nearly all disposed in the axis of the vessel; the circular muscle fibers are confined to a very thin coat beneath the endothelium, or are often entirely absent. Frequently, and especially in the central veins of the adrenal, the coarse bundles of longitudinal muscle fibers project into the lumen of the vessel in a somewhat rugose manner. Whenever two veins unite to form a larger vessel, and at the junction of a central vein with any of its branches, these protuberant muscular bundles are especially prominent. Moreover, Ferguson[10] describes anomalous ves-

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[10] Ferguson, 1905.

In the vicinity of the central veins, small nerve trunks are found, and occasional minute ganglia or isolated nerve cells occur along their course. These are not to be confused with the large ovoid epithelial cells of the medulla.

Blood Supply.—The arteries which supply the suprarenal glands form a *plexus* of vessels in the capsule of the organ and in the neighboring connective tissue. Some of the smaller branches of this plexus, the *capsular arteries*, supply the capsule itself; others enter the organ and are distributed to the cortex and to the medulla. The blood supplied to the capsular arteries, after traversing the capillaries, enters small venules which are *tributary to the lumbar and phrenic*

FIG. 489.—Photomicrograph of Peripheral Portion of Dog's Suprarenal.
C, capsule; G, zona glomerulosa; F, zona fasciculata.

veins. The course of the cortical and medullary vessels has been exhaustively studied by Flint.[9]

The *cortical arteries* enter the zona glomerulosa where they abruptly break up to form a capillary plexus which occupies the connective tissue between the cell columns. Capillary vessels are continued from this plexus through the intercellular reticulum of the zona fasciculata, where they are in intimate relation with the epithelial cells, and reach the zona reticularis. In the zona reticularis the capillaries are collected into thin-walled venules or sinusoids. The intimate association between the cortical cells and the extensive capillary network provides for the vascular escape of the internal secretion of the cortex. These vessels, after some anastomoses, form venous stems which are continued, without further anas-

[9] Flint, 1900

The cortical component arises as a series of buds from the celomic epithelium covering the dorsomedial surface of the cephalic third of the wolffian body. The medulla develops from cells which have migrated from the abdominal sympathetic plexus (celiac plexus), and which elaborate peculiar granules having an affinity for chromium, hence called *chromaffin* or *pheochrome cells*. The ontogenetic process recapitulates almost precisely the phylogenetic history of the suprarenals: In fishes the homologues of the two mammalian components remain separate, and the cortical representative includes a series of bodies, the *interrenal bodies* or organs: the medullary representative, also comprising a series of structures, is known throughout, due to its close topographical relationship to the kidney, as the *adrenal*. The cortex of the mammalian suprarenal gland thus represents the product of fusion of the ichthyoid interrenals. In the groups between fishes and mammals, the association of interrenals (cortical component) and adrenals (medullary component) becomes progressively more intimate; in frogs and salamanders the cortical and medullary primordia are in contact, in reptiles they have begun to merge, in birds they are irregularly intermingled.

The suprarenal is essential to life. According to Crile (1914) the brain is intimately dependent upon the suprarenals; when both glands are excised in the rabbit death follows in eighteen hours, the brain cells meanwhile exhibiting loss of chromophilic substance. The two portions produce different hormones. The cortex is generally believed to elaborate an antitoxic secretion ("cortin," cortico-adrenal extract, *interrenalin*) for neutralization of harmful products of destructive metabolism. The function of the medulla is dependent upon the adrenalin (adrenine, epinephrine) of the pheochrome granules, probably having to do with maintaining the proper tonus of the muscle of the heart and blood vessels, thus underlying blood pressure. Minute amounts of epinephrine in the blood effect a sensitization of the vasoconstrictor nerve endings so that the efferent impulses discharged cause the muscular coats of arterioles to contract vigorously, the result being an increase in blood pressure. The most conspicuous diseases of the suprarenals involve hypersecretion of the medulla, perhaps inducing to arteriosclerosis; and hyposecretion of the cortex, frequently the result of tuberculous lesions, producing a clinical complex known as Addison's disease Euler (1929) explains the hypernormal temperature of fever in terms of overactivity of the adrenals; adrenalectomized animals can not be made to develop fever.

The recent investigations of Swingle[12] *et al.* on dogs leads them to conclude that "The function of the adrenal cortical hormone is the regulation and maintenance of a normal circulating volume of fluid within the vascular system. In the absence of the hormone, fluid is continually lost from the circulation presumably by transudation through the capillary walls, with the result that the adrenalectomized animal is unable to maintain his normal blood volume, and eventually dies from circulatory collapse due to insufficiency of circulating fluid." Bilaterally suprarenalectomized dogs have been *kept alive* for nearly two years by the daily injection with adequate maintenance doses of the cortical hormone Bilaterally suprarenalectomized cats survive for a period of from seven to ten days. Death can be prevented by the injection of cortico-adrenal extract. Britton and Silvette[13] conclude on the basis of their experiments with cats that the factor chiefly responsible for the death of their animals from which the suprarenals were removed is a specific effect on carbohydrate metabolism causing a profound drop in the normal glucose and glycogen levels in the body. They suggest that "the primary action of the [life-preserving] hormone of the adrenal cortex is concerned with the maintenance of normal carbohydrate balance in the body."

[12] Swingle, 1933
[13] Britton and Silvette, 1931.

sels of a venous nature which arise in the medulla, penetrate the cortex, and enter the venous plexus of the capsule; and in these instances the same peculiar distribution of the muscle has been observed in the veins of the capsular plexus.

Lymphatics.—The lymphatics of the suprarenal gland, according to Stilling,[11] form rich plexuses in the zona glomerulosa and in the medulla; elsewhere they are less abundant. They follow the course of the blood vessels and are especially well developed in the vicinity of the central veins.

Nerves.—The suprarenal is well supplied with small sympathetic nerve trunks from the solar plexus. They form a plexus in the capsule from which branches are distributed to the cortex and to the medulla. In the cortex they invest the

blood vessels with a delicate plexus, but have not been found within the epithelial cell columns. In the medulla they are also distributed to the blood vessels and are supplied with occasional small ganglia. Passing from the plexus of sympathetic nerve fibers which invests the groups of medullary epithelium, Dogiel (1894) demonstrated delicate fibrils, supplied with minute varicosities, which penetrate between the epithelial cells and terminate in a manner very similar to that which is characteristic of the epithelial parenchyma of other secreting glands.

Accessory Suprarenals.—These include bodies of three types of structure: (1) bodies consisting exclusively of cortical substance; (2) bodies composed exclusively of medullary substance and indistinguishable from paraganglia; and (3) the true accessory (supernumerary) suprarenals consisting of both cortex and medulla. These bodies are widely

FIG. 491.—SECTION OF PART OF AN ACCESSORY SUPRARENAL (CHROMOPHIL BODY), NEWBORN CHILD.

chr, a chromophil cell. (Schäfer in Quain, *Anatomy*.)

distributed in the vicinity of the suprarenal, sometimes embedded within its substance, sometimes in the kidney, where the ectopic tissue produces a *hypernephroma*, or even in the liver. They vary in size from microscopic bodies to such with a diameter of a centimeter or more. They are frequently found also in connection with the genital system, a rather large representative being almost invariably present in the space between the testis and the epididymis, and in the broad ligament of the female close to the ovary, where it is known as *Marchand's gland* or Marchand's adrenal.

Development and Function.—The suprarenal gland is a composite structure formed by the intimate association of two embryologically distinct primordia: one, the cortical component, of mesodermal, the other or medullary component, of ectodermal origin.

11 Stilling, 1887.

The *follicular epithelium* is typically cuboidal in shape; in young individuals it is somewhat taller than broad. In those follicles which are distended with colloid secretion the epithelium is relatively short; in those which are empty it is taller. Each cell contains a single spheroidal nucleus which lies in the center of the cell. or somewhat toward its basal extremity. This orderly disposition causes the nuclei,
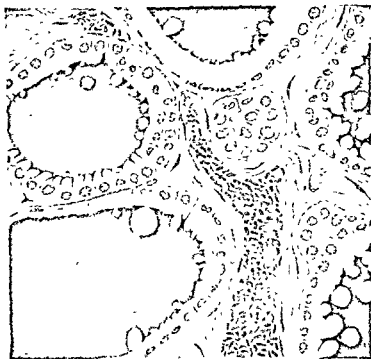
FIG. 492.—SECTION OF SEVERAL FOLLICLES OF THYROID GLAND OF MAN.

The follicles are lined with short columnar and cuboidal epithelium. The lumens contain a vacuolated mass of colloid ×700 (Hardesty)

when seen in sections of the follicle, to appear as a continuous row in the wall of the alveolus, a disposition which is noticeable for its exceptional regularity

The cytoplasm of the epithelium is finely granular and decidedly acidophilic. It usually contains some coarse granules and very small fatty droplets, which generally occupy the extremities of the cells. Minute spheroidal granules which give the color reactions of colloid are also found in the cytoplasm of the epithelial cells Hurthle,[16] by staining with the Biondi-Ehrlich mixture, succeeded in differentiating two types of cell, one lightly staining, the "chief cells," the other a darker colloid-containing type which he designated as "colloid cells." These variations probably only represent different stages of secretion in the same epithelial cell type. Minute intercellular canaliculi occur at the angles between adjacent cells.

In the thyroid of the opossum Bensley[17] also describes two types of cells, namely, the usual epithelial cells and ovoid cells. The latter hold a parietal position in the follicle; they are filled with fine eosinophilic granules which give to these

[16] Hurthle, 1894
[17] Bensley, R. R., 1914.

THYROID GLAND

The thyroid consists of a mass of glandular tubules or follicles, supported by a connective tissue stroma and supplied with a thin but dense fibrous capsule which closely invests the surface of each of its lobes. The thyroid weighs between 1 and 2 ounces.

Connective Tissue Framework.—The capsule of the thyroid consists of dense fibro-elastic tissue, from which trabeculae, containing the larger blood vessels, pass inward and produce an indistinct lobular subdivision. A network of delicate fibers, among which are very few if any elastic fibers, passes from the trabeculae and invests the glandular follicles, forming a delicate basement membrane for their epithelium. Flint [14] has shown that much of this interfollicular connective tissue is of the reticular variety. In it are contained the smaller blood vessels and lymphatics. It also contains a few lymphocytes, which are scattered about in a diffuse manner. It increases in amount with age.

Parenchyma.—The *follicles* of the thyroid are ovoid saccules or short branched tubules with frequent diverticula.[15] They vary greatly in diameter. Many of them present scarcely any lumen; others, by their extreme size (100 to 300 μ), simulate small cysts. All follicles which possess any considerable lumen contain a peculiar acidophil substance, known as *colloid*, which is apparently formed by the secretory activity of the glandular epithelium lining the follicles.

Colloid is a homogeneous or very finely granular substance which stains readily with eosin, taking a very bright tint closely resembling that acquired by the hemoglobin of the red blood cells. Frequently, and especially in specimens which have been fixed and hardened in alcohol, it presents a vacuolated appearance. As a rule the lumen of the follicle is not completely filled with the colloid mass, which is then adherent to the surface of the lining epithelium by delicate thread-like processes; the colloid thus acquires a deceptive appearance of extreme contraction, as if its surface, except for occasional delicate strands, had been drawn away from the epithelium.

Occasionally a single large vacuole, often containing basophil granules or crystalloid particles, occupies the center of the colloid mass in the larger follicles; at other times the colloid material appears to be broken into minute spherules. In general, the ratio of colloid content within the follicle, roughly stated, is in proportion to the age of the individual. The follicles at the periphery of the lobes of the gland are less fully distended than those in the interior.

Embedded in the colloid mass within the follicle, even in the apparently normal thyroid, red blood corpuscles and desquamated follicular epithelium are frequently found, but never in large quantity. Leukocytes are of less frequent occurrence and are more rarely found in the human thyroid than in that of the lower mammals.

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[14] Flint, 1903
[15] Streiff, 1897.

The epithelium rests upon a very delicate reticular basement membrane and is in close relation with the capillaries and lymphatic vessels of the interfollicular stroma. Colloid material, similar to that within the follicles, has been repeatedly found within the lymphatic vessels (Baber, Langendorf, Hürthle) and may be readily demonstrated in most sections of the thyroid. This does not, however, represent the entire internal secretion of the gland.

Blood Supply.—The arteries form a rich plexus in and about the capsule of the thyroid, from which numerous branches penetrate the organ, lying in the connective tissue trabeculae between the lobules; they are distributed to all parts of the gland. They supply a rich intimate capillary plexus in the walls of the follicles. The epithelial cells of the follicles rest directly on the endothelial cells of the capillaries. The veins retrace the course of the arteries. The walls of the smaller venules consist only of endothelium, with a very thin coat of fibro-elastic connective tissue.

Lymphatics.—The thyroid is very abundantly supplied with lymphatic vessels. These form a plexus of very broad lacunar capillaries in the interfollicular connective tissue, where they stand in intimate relation with the follicular epithelium and the blood capillary plexus. From this plexus vessels pass to the interlobular connective tissue, in which they form a second plexus, whence lymphatic vessels pass out of the thyroid in company with the blood vessels and enter the deep cervical lymph nodes.

Nerves.—The nerves of the thyroid are derived from the sympathetic system and are mostly unmyelinated. They accompany the arteries and form a delicate terminal plexus in the walls of the follicles. The finer fibrils of this plexus end in contact with the epithelium. Berkeley (1895) describes also occasional fibrils which apparently penetrated between the epithelial cells.

Development.—The thyroid develops from three primordia, a median and a pair of lateral outgrowths from the primitive pharynx. The median primordium sprouts from the floor of the pharynx at the level of the first pharyngeal pouches. Its site of origin is marked in the adult by the foramen cecum of the tongue. It forms the major portion of the definitive thyroid. The lateral primordia grow from the ventral border of the fourth pouches, they form variable small portions of the lateral lobes.[20, 21] The pyramidal lobe represents the remnant of the embryonic thyroglossal duct, it varies greatly in length in different individuals; it may even retain a partial lumen which may be filled with colloid, but it does not open upon the surface. The original primordia consist of solid cords of cells; the cords subsequently acquire a lumen, and become broken up into lobules and follicles through the invasion of connective tissue According to Kingsbury (1935) the definitive thyroid arises exclusively from the median primordium.

Function.—Removal of the thyroid is followed by serious symptoms and frequently fatal results, particularly in the case of the carnivora. Its internal secretion is necessary for normal metabolism, growth and development. It governs the conditions favoring tissue oxidation (Crile). The essential secretion is something apart from the colloid and iodine content of the gland. According to Crile the active constituent, *thyro-iodine*, is iodine (65 per cent) in a special proteid combination Kendall has named the thyroid

[20] Weller, 1931
[21] Norris, 1937.

cells a character strikingly similar to that of the acidophil cells of the anterior lobe of the hypophysis cerebri. He describes also large needle-shaped crystalloid bodies in the epithelial cells similar to those in the interstitial and Sertoli cells of the testis. In young dogs, from birth to the age of six months, there occur variable numbers of so-called "parafollicular cells," singly disposed or in small groups. They are of relatively large size; they arise in the follicular epithelium, and later migrate into the interfollicular spaces, remaining close to the follicles. They have

FIG. 493—DIAGRAM OF PHARYNX OF HUMAN EMBRYO, SHOWING THE ORIGINS OF THE PRIMORDIA OF THE THYMUS, THYROID AND PARATHYROIDS (EPITHELIAL BODIES.)

Thy^1, earliest position of thyroid primordium; Thy^2, secondary position of thyroid primordium; Tgd, thyroglossal duct; Fc, foramen cecum; $LThy$, lateral thyroid primordia; $Pthy$, parathyroid bodies; pb, postbranchial body; T, tonsil; I, II, III, IV, V, pharyngeal pouches; a, b, first and second branchial grooves (gill clefts); $1, 2, 3$, first, second and third aortic arches in the cores of the branchial arches. The complete wall of the pharynx is only shown at the right, above. (Adapted from Kohn)

a finely granular cytoplasm, oxyphilic in staining reaction. The fate of these cells is as yet unknown.[18] They have been described also in the thyroids of rabbits and cats. The parafollicular cells contain variable amounts of argyrophilic granules. Nonidez disagrees with the suggestion of Zechel [19] that these cells function as a source of new follicles. He concludes that they are "either endowed with secretory capacities or else they represent a type of cell which, after absorbing substances from the colloid, transfer them into the blood stream through the capillary walls."

[18] Nonidez, 1932.
[19] Zechel, 1932

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with the tracheal or laryngeal wall and may be found as high as the hyoid bone
or as low as the border of the thymus. They also vary greatly in size and shape
but usually are of ovoid form and about three to five millimeters in diameter.
Their total weight is not over 5 grains. The superior pair was first described by
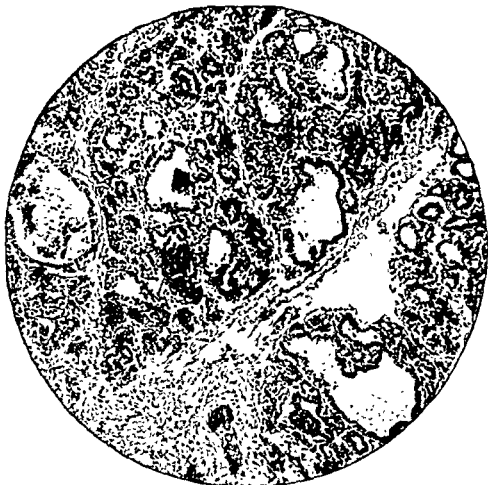
Fig. 494.—From the Border of a Mass of Aberrant Thyroid Tissue of Man, Occurring
in the Region of the Parathyroid Glands.

Hematein and eosin. Photo. ×204.

Sandstrom in 1880. The inferior pair was discovered by Kohn in 1895. Para-
thyroids have now been recognized in all classes of the vertebrates except fishes.

Each parathyroid is invested by a thin capsule of dense connective tissue and
consists of a mass of epithelial cells supported by a delicate fibrous reticulum.
The epithelial cells are of two chief types, designated by Welsh [24] as the "principal"
and the "oxyphil" or acidophil cells.

The *principal cells* are ovoid or spheroidal elements, with a clear vesicular
cytoplasm, a distinct cell membrane, and a large spherical nucleus, whose chromatin

[24] Welsh, 1898

hormone "thyroxin." He used 6550 pounds of fresh thyroid to obtain one ounce of thyroxin. The belief that the thyroid has also an antitoxic rôle is based chiefly on the observation that thyroidectomized animals are extremely liable to certain infections. Gudernatsch's experiments with frog tadpoles show that a thyroid diet accelerates differentiation but inhibits growth: the tadpoles metamorphosed prematurely into diminutive frogs—a result the opposite of that obtained when thymus was fed An enlarged thyroid is commonly known as a goiter. Enlargement may be due to increase in the amount of the connective tissue or of the colloid parenchyma; one results in atrophy of the parenchyma and a condition of hyposecretion, associated with myxedema and in extreme cases in infants with cretinism—an apparently hereditary defect; and the other in hypersecretion, associated with exophthalmic goiter (Graves' disease). In man and animals the thyroid shows a seasonal enlargement related to the sexual cycle.

ACCESSORY OR ABERRANT THYROIDS

These bodies, first described by Zuckerkandl (1879), are widely distributed through the connective tissue of the cervical region. They are most frequently found in the course of the embryonic thyroglossal duct and in the immediate vicinity of the lateral lobes of the thyroid. They present the appearance of embryonal remnants of thyroid tissue, but are found in nearly all individuals.

The colloid follicles of the aberrant thyroids are usually small, though, in the larger specimens of these bodies, they may attain as great a size as those of the thyroid itself. The cell columns without colloid are more numerous than in the thyroid gland, giving to the aberrant bodies a decidedly cellular appearance. Each aberrant mass is usually inclosed by a very thin connective tissue capsule which sends delicate processes between the cell groups. The epithelial cells retain all the characteristics of those of the thyroid gland, and can be readily distinguished from the epithelium of the parathyroid glands with which the accessory thyroid bodies have been frequently confused. Accessory thyroids are also much less vascular than the parathyroids.

PARATHYROID GLANDS

The *parathyroids*, or epithelial bodies, are small glandular bodies of irregular distribution, usually found in relation with the posterior margin of the lateral lobes of the thyroid gland They arise as buds from the dorsal pockets of the third and fourth pharyngeal pouches. Typically four parathyroids are present, the superior pair (parathyroids IV) situated near the lateral, the inferior (parathyroids III) near the median margin of the lateral lobes of the thyroid. The inferior pair in the adult develops from the anterior pair of primordia, and frequently becomes embedded in the thyroid tissue. According to Heinbach [22] their number varies from 2 to 6; exactly 4 occur only in about 50 per cent of all individuals. Norris,[23] in an examination of a large series of embryos and fetuses found no instance in which fewer than four parathyroids were present. They may occur in relation

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[22] Heinbach, 1933

[23] Norris, 1937.

Occasionally, epithelial cells surround a central lumen, in which are small masses of an acidophil substance which resembles colloid in its reactions. This colloidal material is less abundant in the human parathyroid than in that of the lower mammals. Likewise the cystic ducts, lined by columnar or ciliated columnar epithelium, which have been described by Kohn (1897), though of frequent occurrence in the lower mammals are rarely, if ever, found in the human parathyroid.

The connective tissue of the gland is of variable quantity. It forms a thin but dense capsule; occasionally trabeculae extend inward and partially outline indistinct lobules: In many instances a hilus transmits the larger blood vessels by means of vascular trabeculae which radiate to all portions of the organ. A delicate fibrous or reticular stroma invests the individual cells, or the cell groups, when these are present Occasionally the cells are so closely packed that the stroma is scarcely demonstrable.

The *blood supply* of the parathyroid is exceedingly rich Arteries enter from the capsule, or at the hilus, and rapidly break up into a plexus of broad capillary or sinusoidal vessels which follow the fibrous bands of the stroma and are in intimate relation with the epithelium. They are collected into thin-walled venules which retrace the course of the arteries.

Function.—The parathyroids are generally regarded as having a function essential to life. Extirpation in experimental animals, *e.g.*, cat and dog, produces tetany which ends in death. The tetany is associated with a calcium deficiency in the blood. The hormone, *parathormone*, is effective in restoring a normal calcium balance and terminating the tetany. *Parathormone* in its effect on calcium metabolism closely parallels that of vitamin D. Increased secretory activity produces a clinical condition of hyperparathyroidism characterized by decalcification of bone resulting in *osteitis fibrosa cystica.* Since only one hormone has been demonstrated, and both principal and acidophil cells contain similar mitochondria and Golgi bodies, the apparently specific cells may only have the significance of different functional phases. Reference should be made to a paper by Thompson and Collip, "The Parathyroid Glands" (*Physiological Reviews*, 1932, 12).

THYMUS GLAND

The thymus was formerly regarded as an organ of fetal and infantile life, and was believed to attain its maximum development during the second year of childhood. After this time it was thought to become gradually replaced by adipose tissue, its retrograde metamorphosis reaching completion at about the age of puberty. However, Waldeyer (1890) showed that the thymus may persist even in advanced age as a body of considerable size, and apparently functional. The later studies of Hammar [25] and others indicate that the thymus normally continues its development until about the time of puberty. Subsequently it loses slowly in weight, but a true atrophy of the parenchyma with cessation of function, apparently does not occur until about the age of fifty.

[25] Hammar, 1906.

is irregularly distributed and often gives the nucleus a somewhat vesicular character.

The *acidophil cells* are of similar shape but are provided with a small spherical nucleus, which is very rich in chromatin, and a granular acidophilic cytoplasm. *The acidophil are less numerous than the principal cells.*

The distribution of the epithelial cells is subject to considerable variation. Most frequently they form an almost solid epithelial mass, in which capillary vessels are here and there found, the larger blood vessels occupying the coarser bands of the fibrous stroma. In such glands the two cell varieties are either inter-
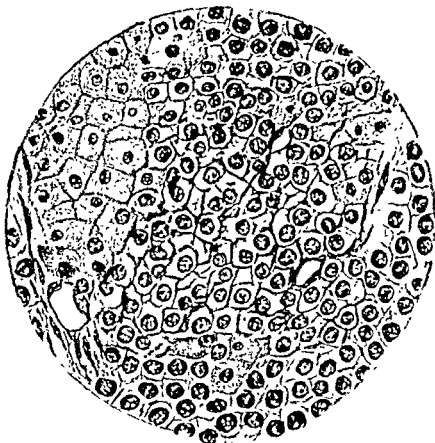
FIG. 495.—PARATHYROID TISSUE OF MAN.

The predominating cells are of the smaller *principal* type. At the left occurs a group of the larger *acidophil* variety.

mingled irregularly, or the acidophil cells may occur in scattered groups which are interspersed among the more numerous principal cells.

In certain instances the epithelial cells are arranged in small alveolar groups which are surrounded by a network of capillary vessels. This arrangement appears to be more frequent in young individuals. The cell groups in this type of gland frequently form branching columns.

of the difference in density, there is a sharp line of demarcation. Frequently, at some point on its circumference, the medulla reaches the surface of the lobule, and at such locations a narrow column of medullary lymphoid tissue connects it with the adjoining lobule.

A delicate reticulum, within the narrow meshes of which are closely packed lymphoid cells, composes the lymphoid tissue of the lobule. That of the cortex and the medulla is alike, except for the fact that the meshes of the reticulum in the cortex are much more crowded with lymphocytes than are those of the medulla. The medulla of each lobule is also characterized by the presence of sev-

eral groups of concentrically arranged epithelioid cells, the *thymic corpuscles* (*concentric corpuscles of Hassall*).

Each thymic corpuscle consists of a large central cell or group of cells, which is surrounded by two to five layers of concentrically arranged flat epithelioid cells. These groups or cell nests are strongly acidophil in their staining reactions, and therefore stand out in marked contrast to the basophilic nuclei of the surrounding lymphoid tissue. A substance simulating the colloid of the thyroid may be present among the cells. Occasionally the central cells become keratized. Since no similar structure occurs elsewhere in

Fig. 497—A Thymic Corpuscle from the Thymus of an Infant. ×665

the body, the concentric corpuscles are absolutely characteristic of the thymus lobule.

The nature of the thymic corpuscles is not satisfactorily understood. According to one hypothesis they represent blood vessels whose lumen has been obliterated by proliferation of its endothelial cells. Another theory regards them as remains of the epithelial columns from which the organ arose in the embryo. They are also interpreted as masses of hypertrophied cells of the reticulum.

The *types of lymphoid corpuscle* which are found in the thymus are similar to those of the lymph nodes, though polymorphonuclear leukocytes are rather more frequent here, and giant cells, mononuclear or multinuclear in form, may be readily found in the medulla of this organ. Pappenheimer regards the specific cells of the thymus as epithelial in character, simulating, but not identical with, lymphocytes.

Blood Supply.—The larger arteries of the thymus are distributed within the interlobular connective tissue. They supply branches to the lobule which penetrate to the medulla, where they form a plexus of sinusoidal capillaries with elongated meshes, and also distribute radiating capillaries to the cortical portion of the lobule. These sinusoidal vessels are highly characteristic of the medulla of the thymus lobule. They unite to form venous radicles of considerable caliber, which leave

It is still uncertain whether the thymus should be classified with lymphoid organs or with endocrine glands. Recent investigations increasingly indicate that it is essentially of lymphoid character but functions, in part at least, as an organ of internal secretion, related to normal growth and sexual development.
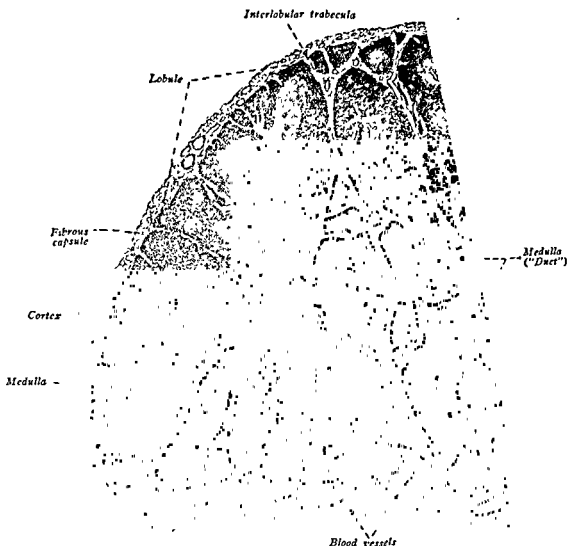
FIG 496.—A SECTION THROUGH SEVERAL LOBULES OF THE THYMUS OF A ONE-YEAR-OLD CHILD
(Hardesty.)

At its maximum the thymus forms a large lymphoid mass, embedded in areolar connective tissue, the trabeculae of which divide the organ into several lobes and innumerable minute *lobules.* Each lobule is surrounded by a thin fibrous capsule, by which it is loosely united to its neighbors.

The lobule consists of a mass of lymphoid tissue, which is dense at the periphery but looser in the central portion It is thus divisible into a dense *cortex* and a loose *medulla,* both composed essentially of lymphoid tissue, but between which, because

eighth in controls; the eyes opened on the second day instead of the fourth as normally; and the testes descended on the fourth day as against the thirty-fifth in controls. The maximal effect was obtained when both parents were treated; no effect follows from treatment of the father only.

CAROTID GLAND

This body was first carefully described by Luschka (1862) and, from its intimate relation to the blood vessels and nerves, is also known as the *glomus caroticum* or *ganglion intercaroticum*. It is about the size of a rice grain. It consists of scattered masses of epithelioid cells, grouped in small spheroidal clumps or *cell*
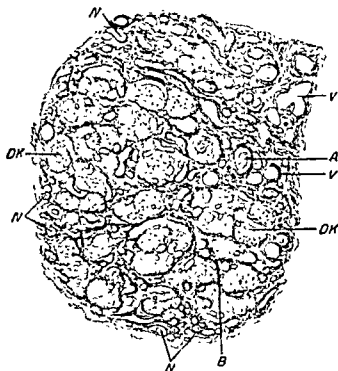
FIG. 498.—CAROTID GLAND OF MAN.

A, artery; *B*, connective tissue; *DK*, aggregations of glandular (pheochrome) cells; *N*, nerve, *V*, vein ×42. (Schaffer.)

balls, embedded in the connective tissue at the point of bifurcation of the common carotid artery. Kohn [32] has described four types of the gland according to the density of its parenchyma—the type found in man consists of scattered cell groups; in the rabbit they are even more diffuse. The carotid gland of a cat consists of a single cell mass, while that of the ape is intermediate between that of the cat and man.

The glandular elements are derived from embryonal ganglion cells from the

[32] Kohn, 1900.

the lobule to join the interlobular veins in the loose connective tissue between the lobules.

Lymph vessels are of frequent occurrence in the interlobular connective tissue, and their branches occasionally penetrate to the medulla of the lobule, but there is nothing corresponding to the lymph sinuses of lymph nodes. Small unmyelinated nerve trunks are also found in the interlobular connective tissue, but seem to be chiefly distributed to the walls of the larger blood vessels.

Development and Function.—The thymus arises as a pair of tubular outgrowths from the ventral aspect of the third pharyngeal pouch, which subsequently become solid and fuse to form a median, flat, bilobed organ lying in the root of the neck and the upper portion of the thorax. According to certain investigators (Stöhr, *et al.*) the lymphoid cells of the definitive organ are derived from the entodermal cells of the initial primordia. The work of Maximow,[26] however, seems to demonstrate that these cells are true lymphocytes and that they have their origin in the surrounding mesenchyma, from the cells of which they differentiate, and from which location they migrate into the thymus primordia—a conclusion confirmed by the more recent study of Badertscher.[27] The original lymphocytes are said to be of the large variety; these give rise through proliferation within the thymus to the smaller types. Among the invading leukocytes are also a small number of polymorphs, and occasionally many eosinophils. The original epithelial primordia continue to grow for a time, and gradually become differentiated into the definitive reticulum of the thymus. Hassall's corpuscles are believed to represent nonreticular remnants of the original entodermal primordia. According to Hammar,[28] these concentric corpuscles are derived from hypertrophic entodermal reticular cells. They first appear early in fetal life, and continue to form and increase in size during infancy. They are interpreted by some as thymic elements of internal secretion. The thymus is commonly regarded as a hemopoietic organ, but its activity is limited to the formation of lymphocytes and possibly a small number of granulocytes. Beard (1900) views it as the original source of leukocytes. The proliferative foci are the cortical portions of the lobules; the medulla does not correspond to the germ centers of lymph nodules, but is probably an area of leukocyte dissolution. The thymus does not seem to be an organ essential to life. Extirpation in dogs and guinea-pigs is not followed by death. However, some of the experimental evidence indicates a reciprocal functional relationship between the thymus and certain of the organs of internal secretion, especially the sex glands. This suggests a secretory rôle; a conclusion supported by the results of Allen's[29] experiments in which thymus fed to frog tadpoles, delayed sexual maturity, and in the male cause degeneration of the testes. But it is also recorded[30] that removal of the thymus in twenty-five-day-old albino rats produced *no significant changes in length of body and tail or in weight* of body, head, hypophysis, suprarenals, thyroid, testes and epididymides. Thymectomized animals between puberty and ninety-days were capable of inseminating normal females.

By continuous treatment of successive generations of albino rats by intraperitoneal injections with thymus extract Rowntree, *et al.*,[31] produced increasing acceleration of rate of growth and development. The precocity became pronounced in the third and later generations. Animals of the fifth generation weighed more than double normal between the third and twentieth day. In these rats the teeth erupted on the first day as against the

26 Maximow, 1909.
27 Badertscher, 1915.
28 Hammar, 1921.
29 Allen, 1920.
30 Hashimoto and Freudberger, 1939
31 Rowntree, Clark, Hanson and Steinberg, 1934.

According to Stoerck,[35] the cells of the coccygeal body do not give the pheochrome reaction at any period of life. They are believed to bear no genetic relation to the sympathetic nervous system. Schumacher regards the epithelioid
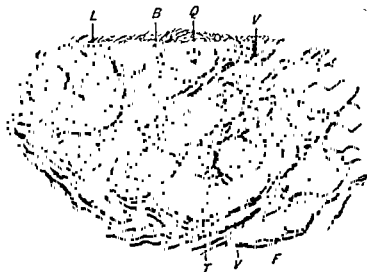
FIG. 499—COCCYGEAL GLAND OF MAN, SHOWING CORDS OF GLANDULAR CELLS.

B, connective tissue; *F*, fat cell; *L*, blood vessel in longitudinal section; *Q*, blood vessel in cross section; *T*, cell cord; *V*, vein. ×110 (Schäffer.)

cells as a transformation of the smooth muscle cells of the arterial vessels; others interpret them as modified endothelial cells of the blood vessels.

PARAGANGLIA

The so-called chromaffin system includes besides the medulla of the suprarenal and the carotid gland, other larger and smaller groups of chromaffin cells (pheochrome organs) derived from embryonic sympathetic neurons and scattered along the entire sympathetic nervous system, the *paraganglia*. They are therefore present in many organs which receive a considerable sympathetic innervation, *e.g.*, kidney, liver, uterus, testis, etc. Chromaffin tissue composed of widely scattered cells occurs also in the sympathetic trunks, particularly the various plexuses, among the definite neurons of this system.

The largest paraganglia (organs of Zuckerkandl) occur in close relation to the inferior mesenteric artery, one on either side. Other smaller groups are found in relation to the abdominal aorta. Busachi[36] has described chromaffin tissue in the human heart; and Thulin[37] reports a paraganglion in the striped muscle of the upper portion of the esophagus of man. In typical paraganglia the polygonal cells are arranged in irregular cords which form a fine-meshed network, the areolae of

[35] Stoerck, 1906.
[36] Busachi, 1912
[37] Thulin, 1914.

ninth and tenth cranial nerves and from the cervical sympathetic trunk. They are ovoid cells with finely granular cytoplasm and a spheroidal, somewhat vesicular nucleus. Some of them may contain chromaffin granules. Because of its genetic relationship and histologic similarity to a sympathetic ganglion, Kohn proposes the name, *paraganglion caroticum*. Its function is apparently similar to that of the other organs of the chromaffin system, and probably chiefly dependent upon the presence of adrenalin.

The carotid gland is richly supplied with capillary blood vessels and small unmyelinated nerve trunks. The capillaries are in intimate relation with the glandular epithelium. The nerve fibers are supplied by the glossopharyngeus; they terminate in intimate relation with the parenchymal cells. The carotid gland has anatomic connection with the carotid plexus in the adventitia of the carotid sinus, a dilatation at the point of origin of the internal carotid artery. The fibers of this plexus meet in a small nerve (of Hering) which connects with the glossopharyngeal and vagus nerves. The sinus is sensitive to mechanical and chemical stimuli.

Later investigators have cast doubt upon the endocrine nature of the carotid body. The number of chromaffin cells varies in different species; they may be lacking entirely. The stroma is derived from the mesenchyme of the third branchial arch. In the calf and the rat the parenchyma has origin from both the cervical sympathetic and the cranial nerves, represented by the ninth and tenth cranial nerves respectively.[33] The histogenesis of the carotid body of man is essentially identical except that, in the opinion of Boyd,[34] "mesodermal cells persist to form a considerable portion of the essential cells in the adult structure." Boyd thinks that the absence of a true chromaffin reaction in the essential cells of the carotid bodies of many mammals (man, rabbit, dog, cat, rat, horse) and the presence of only occasional chromaffin cells in the carotid bodies of the ungulates indicates "that the function of the carotid body will not be found in the secretion of adrenalin."

COCCYGEAL GLAND

This small body—2.5 millimeters in diameter (Eberth)—was discovered by Luschka in 1860. Its structure closely resembles that of the carotid gland. It usually consists of several minute groups of epithelioid cells which are in relation with the terminal branches of the middle sacral artery. It is richly supplied with broad capillaries or sinusoids and hence is also known as the *glomus coccygeum*.

The parenchymal cells of the organ are ovoid elements which are closely packed about the walls of the blood vessels in groups or short columns inclosed by delicate sheaths of connective tissue. The origin and function of these cells are unknown. No chromaffin cells have yet been certainly demonstrated. The organ is embedded in the dense connective tissue at the tip of the coccyx. Its general structure only suggests an internal secretory function.

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[33] Smith, 1924.
[34] Boyd, 1937.

about 5 millimeters in length immediately behind the vomer. This is frequently the initial seat of tumors.

Histologic Structure.—The hypophysis is usually described as consisting of three portions: (1) the *anterior lobe* or glandular portion; (2) the *intermediate portion* or boundary zone; and (3) the *posterior lobe*, or nervous portion (neurohypophysis). The more critical investigations of Tilney,[38] including careful reconstructions of a number of mammalian hypophyses, show that this description is incomplete. The form, extent, relation and genetic significance of the *pars intermedia* had apparently hitherto not been fully appreciated, though Herring (1908) had
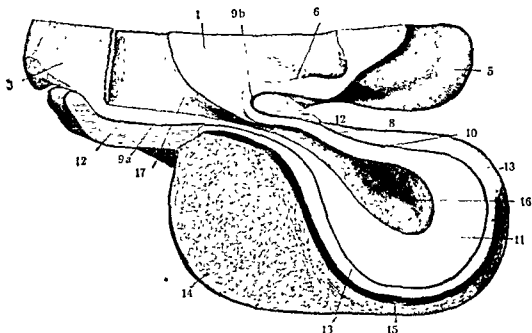
FIG. 501.—SAGITTAL VIEW OF A WAX RECONSTRUCTION OF THE HYPOPHYSIS CEREBRI OF THE ADULT CAT.

1, third ventricle; *9a* and *b*, eminentia saccularis; *6*, area premammillaris, *5*, corpora mammillaria, *12*, pars tuberalis, *8*, recessus infundibuli, *10*, infundibulum; *13*, pars infundibularis; *16*, recessus processi infundibuli; *11*, processus infundibuli; *15*, lumen residuale, *14*, pars distalis; *17*, recessus tuberis, *3*, optic chiasm (Tilney).

already called attention to the fact that it comprised two histologically different areas. Tilney divides the hypophysis into *pars neuralis* (pars nervosa), and *pars buccalis*. The *pars neuralis* consists of three distinct elements: (1) the *eminentia saccularis* of the *tuber cinereum;* (2) the *infundibulum;* and (3) the *infundibular process.* The *pars buccalis* consists of two elements: (1) the *pars juxta-neuralis* in close relation with and investing the neural portion; and (2) the *pars distalis.* A cleft, the *residual lumen* (intraglandular cleft), remnant of the original cavity in the buccal diverticulum, appears between the two Further analysis of the juxtaneural portion of the gland reveals two histologically different parts: (1) the *pars*

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[38] Tilney, 1913

which are occupied by sinusoidal blood vessels, upon which the cells rest directly without the intervention of a basement membrane. The spherical nucleus is poor in chromatin; the reticular cytoplasm contains the pheochrome granules. The internal secretion of the paraganglia depends upon the adrenalin content of the granules. Adrenalin produces a contraction of involuntary muscle. Its function appears to be to maintain the proper tonus of the blood vessels.

HYPOPHYSIS CEREBRI (*Pituitary Body*)

The *hypophysis* is a gland of composite structure, arising from the association of two originally distinct primordia; one taking origin as a median dorsal diverticulum (Rathke's pouch) from the primitive mouth, the other as a medial ventral evagination from the second cerebral vesicle (third ventricle) or diencephalon.

Both components are thus ectodermal. The cerebral flask-shaped element invaginates the buccal element and modifies the original bulbar shape of the latter into that of a cup. The buccal connection disappears, while the cerebral connection persists as the infundibular stalk of the definitive structure.

The hypophysis is present as an essentially similar organ in all craniates. In man it measures about 12 millimeters in the transverse, about 7 millimeters in the sagittal, and about 5 millimeters in the vertical diameter. It has an inverted mushroom shape, the stalk or *infundibulum*, a hollow funnel-shaped structure lined with ependyma, attaching it to the brain, while its head is lodged in the sella turcica of the sphenoid bone. It weighs about one-sixteenth of an ounce. The hypophysis was known to
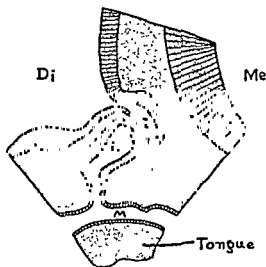
Fig. 500—Median Section through the Primordia of the Hypophysis Cerebri of a 10 Millimeter Cat Embryo (Bonnet.)

D₁, diencephalon; *Me*, metencephalon; *M*, mouth; *R*, Rathke's pouch (pituitary primordium); *I*, infundibulum. ×50

the early anatomists as the *pituitary gland* (Vesalius, 1543), and was supposed to function as an excretory organ in the elimination of mucus (pituita) from the brain by way of the nose. The term pituitary gland is now generally applied only to the larger anterior component or *epithelial lobe*, the posterior component or *neural lobe* is designated the *infundibular process*; the term *hypophysis* is applied to the associated elements. But hypophysis and pituitary body are still often used synonymously. The neural and glandular tissues are said to be connected with each other by means of nerve fibers, probably sympathetic, connective tissue, and blood vessels Certain investigators have described accessory pituitary bodies. Thus Haberfeld (1909) finds in man at all ages a "pharyngeal pituitary," a solid cord of neutrophilic cells

Pars Buccalis (Pars Glandularis).—PARS JUXTANEURALIS.—Pars Tuberalis.—
The pars tuberalis consists of cell cords connected into a continuous network. In
many animals it contains numerous alveoli, follicles or acini, enclosing colloid. In
man alveoli appear first in the fifth month after birth. Guizzetti [40] describes three
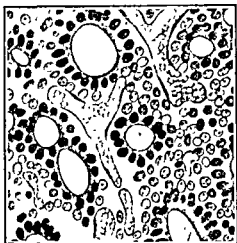
FIG. 502

FIG. 503

FIG. 502.—PARS TUBERALIS, HYPOPHYSIS OF CAT. (Tilney.)
FIG. 503.—PARS INFUNDIBULARIS, HYPOPHYSIS OF CAT. (Tilney.)
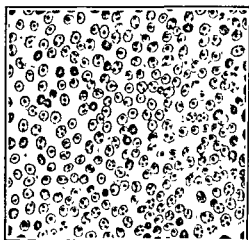
types of cells in the pars tuberalis of man: (*a*) predominating chromophobes;
(*b*) basophils; (*c*) pavement cells. The chromophobes show typical mitochondria
and a Golgi apparatus. The blood vessels are large and thin walled and drain
through "portal" veins into the sinuses of the pars distalis.

Extracts of the pars tuberalis are said to pro-
duce diuresis. Atwell's [41] latest studies of this
constituent of the hypophysis lead him to con-
clude that it still remains an enigma; "whether it
possesses a definite function or is merely a rudi-
mentary structure cannot yet be stated with
certainty."

Pars Infundibularis.—Here the cells are ar-
ranged in a dense stratum several layers deep.
Occasional acini (cysts) occur, but they are
smaller than in the *pars tuberalis* and are lined
with only a single layer of low cuboidal cells.
These cells contain large vesicular centric nuclei
surrounded by a considerable layer of faintly
basophilic granular cytoplasm. Blood vessels are
very meager and thin-walled.
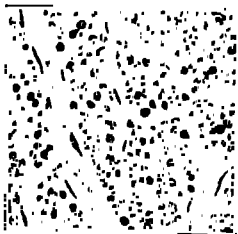
FIG. 504.—PARS DISTALIS, HYPO-
PHYSIS OF CAT. (Tilney.)

PARS DISTALIS (*Anterior Pituitary*).—This portion is surrounded by a robust
fibrous capsule continuous posteriorly with a thinner investment for the neural
lobe. Delicate trabeculae traverse the parenchyma and support the very abun-

40 Guizzetti, 1925.
41 Atwell, 1936.

infundibularis completely investing the *infundibulum* and the *infundibular process*, and (2) the *pars tuberalis*, which surrounds the *eminentia saccularis*.

The following outline presents this analysis in résumé:

HYPOPHYSIS CEREBRI

I. Pars Neuralis: (Posterior lobe, Neurohypophysis)
    1. Eminentia Saccularis (Median eminence)
    2. Infundibulum
    3. Processus infundibuli

II. Pars Buccalis seu Glandularis:
    1. Pars juxtaneuralis (Intermediate portion)
        (a) Pars tuberalis
        (b) Pars infundibularis
    2. Pars distalis (Anterior lobe, Adenohypophysis)

The pars infundibularis makes its appearance almost immediately after the anlage of the buccal portion of the hypophysis is formed. The pars tuberalis arises as a relatively late structure. It has its origin in two secondary diverticula or sprouts from the body of the pituitary sac (buccal evagination). These sprouts, the lateral processes, ultimately fuse with each other across the median line, displace the body of the pituitary sac ventrad and thus secondarily assume their juxtaneural position. The juxtaneural portion of the hypophysis is intimately connected with the neural portion by means of nerve fibers, blood-vessels and connective tissue processes. Attempted separation consequently necessarily includes laceration of neural elements.

Accordingly, complete removal of the pars buccalis would seem to be impossible without the attendant removal of portions of the pars neuralis. This must be taken into account in interpreting symptoms following removal of the anterior lobe of the hypophysis.

Pars Neuralis, Infundibulum.—This consists of fusiform and multipolar neuroglia cells and fibers. A substance resembling colloid is also occasionally present. Small nerve cells have been reported, but their presence seems doubtful. The glia cells generally have a single nucleus, but two or more may appear. The protoplasm is finely granular, and occasionally contains pigment granules, which seem to be more abundant in aged specimens. Delicate and coarse glia fibers extend through the protoplasmic portions of the cells, frequently terminating the cell processes (Fig. 505). The larger highly branched neuroglia cells with cytoplasmic granules are presumably specialized cells ("pituicytes") for the elaboration of the hormone, pituitrin.

Gersh [39] recognizes specific cells in the neurohypophysis to which he ascribes the production and secretion of an antidiuretic substance. These glandular cells he discriminates from neuroglia cells elsewhere in the nervous system by their characteristic cytoplasmic content of lipoid granules and spherules.

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[39] Gersh, 1939.

topographical segregation and more probably designates an actual functional division. True chromophobes, cells which stain only faintly and with difficulty in either acid or basic dyes—and probably functional phases of acidophil and basophil cells —appear first only in the higher sauropsids (Tilney) The nuclei of the several cell types are large and deeply staining. The cells in great part rest directly upon the endothelial walls of the capillaries. The blood vessels are said to contain colloid.

FIG 506—PARS DISTALIS OF THE HYPOPHYSIS OF A PIG.

c, alpha cell, *b*, beta cells; *c*, chromophobe cell. Safranine-acid violet stain. (Maurer and Lewis.)

Rasmussen [42] gives the average proportion of the three chief varieties of cells in the pars distalis of the normal adult human male as: chromophobes (neutrophils), 52 per cent; acidophils, 37 per cent; basophils, 11 per cent. Women are said to have a distinctly higher proportion of acidophils (43 per cent) than men, and with a lower percentage of chromophobes (49 per cent) and of basophils (7 per cent). [43] An increase of basophils in dementia praecox (17 per cent) and other forms of psychosis (28 per cent) has been reported. [44] During pregnancy there occurs a marked secretory activation of both basophils and acidophils and there appears a characteristic cell with fine acidophilic granules, the "pregnancy cells" of Erdheim Castration causes an increase in the number of basophils and the appearance of a specific type, the so-called "castration cells". These are enlarged basophils with a globule of clear colloid-like substance, giving the cells the semblance of a signet-ring.

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[42] Rasmussen, 1929; [43] Rasmussen, 1933; [44] McCartney, 1929

dant plexus of arteriovenous sinusoidal blood spaces. The peripheral cells of the pars distalis constitute a narrow zone of almost exclusively *basophilic cells* (*beta cells*). The cells of the main central portion are arranged in dense convoluted anastomosing cords. The cords comprise axial and parietal cells. The parietal cells are the larger, of polygonal shape, and with a granular cytoplasm deeply acidophilic. These are the eosinophilic or *acidophilic* (chromophil) cells (alpha
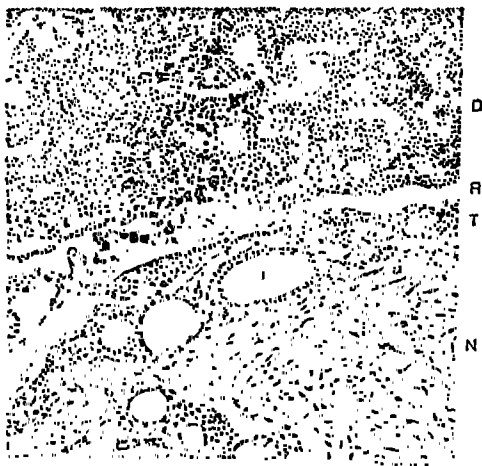
FIG. 505—SECTION OF HYPOPHYSIS CEREBRI OF DOG, SHOWING PORTIONS OF PARS DISTALIS (*D*) OF BUCCAL LOBE, RESIDUAL LUMEN (*R*), PARS JUXTANEURALIS (PARS INTERMEDIA), (*T*) AND PARS NEURALIS (*N*).

Note the abundant large blood sinuses in the glandular or buccal portion, and the tubules in the pars tuberalis (referring to the portion next the tuber cinereum). The pars neuralis is largely of neurogliar composition.

cells). The axial cells are smaller; their cytoplasm contains neutrophilic granules. These are the *chief*, or chromophobe cells. The so-called chromophils and chromophobes of the earlier terminology, which was based simply upon a difference in the degree of tingibility, probably represent merely different functional phases of the same cell type. The classification of the cells as acidophils and basophils, a distinction based upon a more precise microchemical difference, accords with a

In the hypophysis of the ox, Wulzen has described a cone-shaped structure in connection with the pars intermedia projecting medially into the residual lumen and resembling in cellular constitution the pars glandularis but differing in having finer connective tissue septa and smaller acini.

Function.—The hypophysis cerebri is essential to health and normal growth. It is the "master gland" of the endocrine system. At least eleven different hormones are attributed to this gland: seven to the pars distalis, two to the pars nervosa, one to the pars intermedia, and one to the pars tuberalis. The specific cells responsible for these hormones have not yet been definitely identified. The best known of the hormones of the anterior lobe is tethelin, the growth hormone. This hormone is believed to be elaborated by the neutrophilic cells of the pars distalis. Hypersecretion (hyperpituitarism) of the growth hormone produces the pathologic conditions of acromegaly and gigantism; deficient secretion (hypopituitarism) inhibits complete development of the skeleton and results in dwarfism and infantilism. It has been repeatedly shown [50, 51, 52] that administration of *anterior lobe substance* to frog tadpoles accelerates growth and metamorphosis Evans [53] produced gigantism in rats by similar means. He injected anterior hypophyseal substance intraperitoneally over a period of 333 days The experimental animal weighed at the end of that time 596 grams, the healthy litter mate control weighed only 248 grams

The six additional secretory products of the pars distalis are the sex (gonad stimulating or *gonadotropic*) hormone (gonadokinin); the milk (lactogenic, *mammotropic*) hormone; the *adrenotropic* hormone, which stimulates the secretory function of the suprarenal cortex; the *thyreotropic* hormone, which controls the action of the thyroid gland, the so-called *diabetogenic* hormone, which appears to be antagonistic to insulin; and the *hematopoietic* hormone, which controls the blood-forming function of the bone marrow. Of the three recognized varieties of cells (neutrophils, eosinophils and basophils) of the pars distalis, one or several must be responsible for more than one hormone. Gonadokinin is believed to be produced by the basophil. According to Gerhart [54] the sex hormone (hebin) is itself a mixture of two antagonistic hormones in the female, prolan A and prolan B. Prolan A is the *follicle stimulating hormone*, causing maturation of the ovarian follicles, stimulating ovulation and inducing the secretion of *folliculin* Prolan B is the *luteinizing hormone*, which causes the transformation of the follicle into a corpus luteum with the production of lutein. In the male the gonadotropic hormone stimulates the testis, both as regards spermatogenesis and the function of the interstitial cells

Flaks, et al [55] ascribe to the hypophysis also a myelotropic or hematopoietic hormone which acts directly on bone marrow. Prolonged oral administration of the anterior lobe of the hypophysis is said to produce in rats an increase in the number of reticulocytes, increase in the total red cell count and conversion of gray into red marrow.

Injection of extract of the *posterior lobe* (pituitrin) into the blood vessels produces a rise of blood pressure accompanied by diuresis, believed to be due to a stimulation of the smooth musculature of the blood vessels. In its effect upon smooth muscle, particularly of the uterus, which it stimulates to sharp and prolonged contraction, it resembles very closely the secretion of the medulla of the suprarenal gland (*adrenalin*). *Pituitrin* is now extensively used in practical medicine and especially in obstetrics Pituitrin causes contraction of smooth muscle supplied by parasympathetic nerves (colinergic fibers); adrenalin causes contraction of smooth muscle supplied by sympathetic nerves (adrenergic fibers)

[50] Allen, 1920; [51] Uhlenhuth, 1923; [52] Hogben, 1923; [53] Evans, 1924; [54] Gerhart, 1932; [55] Flaks, Himmel and Zlotnik, 1937.

Comparative histologic studies indicate that the pituitary gland has a twofold activity, one part dependent upon the basophils, the other upon the acidophils. The residual lumen is lined only with basophils, and occasionally contains colloid Comparative morphology indicates that the neural portion may represent an original special sense organ. It has been suggested by Tilney [45] that the basophils contribute their secretion by way of the residual lumen and the infundibular process to the cerebrospinal fluid, and the acidophils directly through the blood spaces.

Blood Supply.—The pars distalis receives from eighteen to twenty small arteries which converge to it from the circle of Willis. The blood channels within the lobe are sinusoidal in character and drain into a venous circle overlying the circle of Willis. The circulation has been studied in greater detail in dogs,[46] cat [47] and monkey. It is closely similar in the hypophysis of man. The blood supply of the hypophysis is independent from that of the brain proper, except for a few capillary anastomoses. The arteries comprise two groups, the *superior* and *inferior hypophyseal arteries,* branches of the internal carotids and the circle of Willis. The superior arteries (arterioles) send branches to the stalk and anterior lobe, and contribute a branch to the infundibular process. The inferior arteries supply the process and the pars intermedia exclusively, but connect through capillary branches with the vessels of the stalk and anterior lobe. *Portal venules* arising from plexuses of the pars tuberalis and infundibular stalk connect with sinusoids in the anterior lobe, which drain through venules into the adjacent dural cavernous sinuses. Venules from the periphery of the pars tuberalis drain into basilar pial veins.

Nerve Supply.—The nerve supply to the hypophysis in the dog is, according to Dandy,[48] derived from the carotid plexus of the sympathetic system, which connects with the oculomotor and optic nerves. The innervation of the anterior lobe is described as abundant, that of the posterior lobe as very scanty. The fibers are thought to be secretory in character. The posterior lobe in man receives a rich supply of unmyelinated fibers from the nerve centers of the tuber cinereum.

Dandy described also a small spherical body which he names *parahypophysis* in connection with the under central surface of the hypophysis, resting in a depression in the floor of the sella turcica. This was found in over 80 per cent of dogs examined. It is interpreted as a remnant of the embryonic Rathke's pouch. It is said to vary greatly in size and histological character, occasionally extending to the "pars intermedia," and to have an individual blood supply and possibly also a nerve supply. A parahypophysis has not yet been reported for man.

Certain investigators have described ciliated columnar cells in the epithelium lining the residual lumen; also patches of branched tubular glands, especially common in young children, projecting from the pars juxtaneuralis into the posterior lobe.[49]

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[45] Tilney, 1911
[46] Dandy and Goetsch, 1911.
[47] Wislocki, 1937.
[48] Dandy, 1913
[49] Rasmussen, 1929.

FIG. 509.—AREA FROM PINEAL BODY OF A YOUNG BOY.

Shows the stellate neuroglia cells (fibrous astrocytes) with processes ending in expansions in the interlobular tissue (above) and in the adventitia of a blood vessel (below at right). (After del Rio Hortega.) Hortega regards these parenchymatous cells as proper for the pineal body

FIG. 510.—PHOTOMICROGRAPH OF PERIPHERAL REGION OF PINEAL BODY OF A YEARLING SHEEP, TO SHOW THE CHARACTER OF THE PARENCHYMA, THE NEUROGLIA CELLS AND FIBERS, AND THE INTERNEUROGLIA CELLS.

The intermediate portion yields a substance which stimulates uterine contractions, but of relatively slight degree, and the secretion of milk.

The work of Bugbee and Kamm [56] has given a more precise analysis of the functions of the posterior lobe. It reveals that this lobe contains two distinct active principles; an *oxytocic* principle (*alpha-hypophamine, oxytocin, pitocin*) which causes contractions of the uterus, and a *pressor* principle (*beta-hypophamine, vasopressin, pitressin*) which stimulates peristalsis in the gastro-intestinal tract and affects the muscle of the renal blood vessels. Pitressin also has an antidiuretic effect.

EPIPHYSIS CEREBRI

(*Pineal Body*)

The epiphysis (*pineal body, pineal gland or conarium*) may be regarded provisionally as an endocrine gland. Its glandular function may be of importance only during late fetal and infantile (or prepubertal) life, when it may control
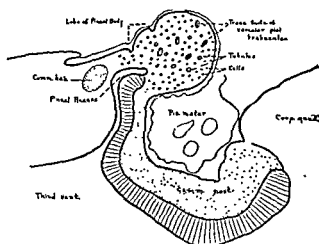
FIG. 507.   FIG. 508.

FIG. 507.—SEMIDIAGRAMMATIC REPRESENTATION OF A MEDIAN LONGITUDINAL SECTION THROUGH THE EPIPHYSIS OF A 17 CENTIMETER SHEEP FETUS.

FIG. 508.—CELLS FROM THE PINEAL BODY OF AN 11 CENTIMETER SHEEP FETUS.

a, two neuroglia and one interneuroglia cell; *b*, various forms and sizes of intracellular melanic granules. ×1500.

normal growth. The mammalian epiphysis has been known to anatomists as a probable gland since the time of Galen (200). It has excited interest and been the subject of much speculation for centuries. Descartes (1649) regarded it as the seat of the "soul." Notwithstanding much study, it is still but imperfectly understood, and even its histological makeup is to some extent in dispute.

Histologic Structure.—The epiphysis cerebri is divided imperfectly into lobes by trabeculae of fibro-elastic connective tissue provided by the pia mater capsule.

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[56] Bugbee and Kamm, 1928.

cells are characterized by pigment granules. In aged specimens the pigment is for the most part present in the shape of extracellular clumps, also in these stages the connective tissue is relatively much more abundant, and the interneuroglia cells are rare. The interneuroglia cells are probably less highly differentiated neuroglia cells, both types originally arising from ependyma. The interneuroglia cells also contain granules and vacuoles of a lipoid nature, perhaps degenerative
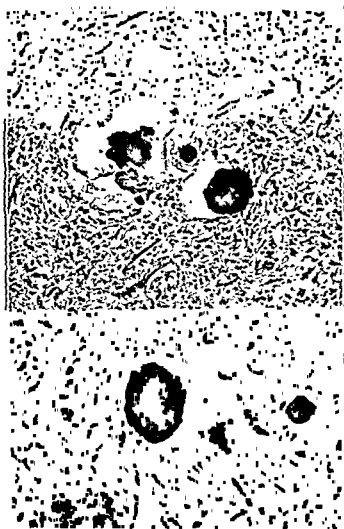
FIG. 513.—SECTION OF PINEAL BODY OF AN OLD SHEEP, SHOWING "BRAIN SAND" (ACERVULUS) IN THE PARENCHYMA.

in significance; no pheochrome granules are demonstrable. Involution begins about the age of seven years in man and ends about the age of puberty, though regressive histological changes proceed throughout life. Adult corpora pinealia present very variable histologic pictures.

In older specimens large lamellated masses of *brain sand* (*acervulus cerebri*, appear, consisting chiefly of calcium carbonate and magnesium phosphate. These specimens are also characterized by large edematous areas. The interneuroglia cells have been variously designated as pineal cells, epithelial cells, lymphoid cells

These support the larger blood vessels. The finer trabeculae shade into the fundamental reticular tissue which supports the parenchyma and the capillaries. The larger vessels are surrounded by considerable spaces, perhaps lymphatics. The parenchyma is aggregated into uncertain follicular masses and consists of two distinct types of cells: neuroglia and interneuroglia (secretory cells?). The
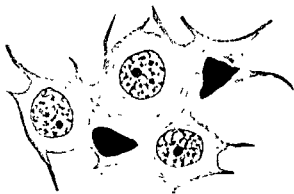
FIG. 511.—TWO NEUROGLIA AND THREE INTERNEUROGLIA CELLS FROM THE PINEAL BODY OF A LAMB. ×1500.
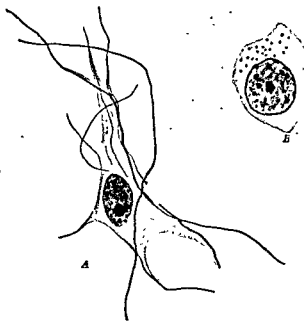
FIG. 512.—CELLS FROM PINEAL OF YEARLING SHEEP.

A, neuroglia cell and fibers; B, interneuroglia cell with melanic pigment granules. ×1500

abundant neuroglia fibers appear to blend intimately with the connective tissue framework of the structure. The interneuroglia cells are oval and polygonal, with a vesicular nucleus, and apparently lack a cell membrane. The neuroglia cells are fusiform or stellate, with denser, more deeply staining nuclei, and glia fibers in the cytoplasm. Transition forms are abundant. In young sheep both types of

Function.—Injection of pineal extract of sheep into the blood of certain mammals produces only very slight effects. These, however, are fairly uniform, but very transient. The most conspicuous effect is a slight fall of blood pressure. There is also a slight improvement in the beat of the isolated cat's heart, a transient diuretic effect in the rabbit and a slight irregular respiratory effect in dog, cat and sheep [57] These results are, to some extent, the reverse of those obtained with extracts of the hypophysis, and suggest a compensatory or antagonistic regulatory functional relationship. Extirpation experiments have not yet yielded perfectly satisfactory results. The evidence, however, indicates a functional rôle which is negligible or nil. Clinical evidence combined with autopsy findings indicate symptom complexes associated with pineal tumors or other structural alterations in general like, but of reverse relationship, to those present in the case of hypophyseal alteration; i.e., the symptoms of hypopinealism are in general those associated with hyperpituitarism, and those of hyperpinealism like those accompanying hypopituitarism. The symptoms associated with morbid conditions of the pineal may possibly be the inherent result of pressure (or undue relaxation) upon the hypophysis transmitted through the third ventricle with which both pineal and hypophysis are connected Certain symptoms may also be due to a blocking of the aqueduct, and to pressure upon the corpora quadrigemina. A conservative estimate of all the evidence indicates very meager, if any functional activity, probably never essential to life. The practical absence of the pineal body in the opossum adds further support to this conclusion, as also its occasional disappearance, except for a mere shell, in apparently normal cats. Biedl (1910), however, arrives at the conclusion that the pineal body is an organ of internal secretion with metabolic significance limited to the young. Its general histological structure, and profuse vascularity, certainly suggest a glandular function. On the basis of feeding experiments with bullocks' pineals on certain laboratory animals and mentally defective children, Dana and Berkeley [58] venture to suggest a relationship of pineal function in the young to bodily nutrition, including the development of the genital organs, the deposit of subcutaneous fat, general growth and mental progress. Removal of the pineal in chickens of from twenty-five to forty-two days produced premature development of both primary and secondary sex characters in both cock and hen.[59] The pineal is a common seat of cysts and tumors, frequently gliomata.

Complete removal of the pineal body in the rat between the ages of one to three days produced no effect on the rate of growth, age of puberty or the weight of the hypophysis cerebri, thyroid, suprarenals or thymus in either sex, nor did it affect the weight of the testes in the male, nor the occurrence of normal estrus cycles in the female [60]

By intraperitoneal injections of pineal extract through successive generations Rowntree, et al,[61] produced in albino rats specific biologic effects in the third to the fifth generations. The growth rate was retarded by approximately one-half but the rate of differentiation was accelerated and the onset of adolescence was hastened. The accruing retardation of growth and accruing acceleration in gonadal and bodily development produced a condition of "precocious dwarfism" as the outstanding result of these experiments

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[57] Jordan and Eyster, 1911

[58] Dana and Berkeley, 1913.

[59] Izawa, 1923

[60] Andersen and Wolfe, 1934

[61] Rowntree, Clark, Steinberg and Hanson, 1936.

and secretory cells. Certain workers claim to have distinguished, in certain mammals, two types of cells, basophils and acidophils. Occasional smooth and striped muscle fibers have also been described in a few forms (*e.g.*, ox). No nerve cells are demonstrable. Sympathetic *nerves* accompany the blood vessels; and a few of the myelinated type are found near the attached portion, probably taking origin from the habenular and posterior commissures. The *blood supply* is profuse. It takes origin from the pial vessels which are in union with the blood vessels of the tela choroidea anteriorly. The vessels follow the ramifications of the pial septa. In the sheep the capillaries frequently terminate in the form of tangled loops or "glomeruli" within spaces surrounded by more compact parenchyma (follicles). Cross-sections of the coarser trabeculae show a pair of vascular comites.

Development.—The epiphysis cerebri arises as an ependymal diverticulum from the roof of the diencephalon. The apical cells proliferate and undergo differentiation into neuroglia and interneuroglia cells. The latter may perhaps assume secretory activities, but no convincing cytological evidence appears indicative of such function apart from numerous melanic granules—which, however, are present in all of the cells in early stages of development—and certain lipoid granules and spherules. In the sheep numerous cysts, lined by tall columnar (ependymal) cells appear at half term (21 centimeter stage). The cysts contain a coagulum. The cysts progressively disappear, apparently through pressure from proliferating cells without, only a few persisting to birth and occasionally after. In the sheep the cysts arise through accumulations of fluid, compelling a cellular arrangement simulating acini, not as tubular outgrowths from the original lumen, as is apparently the case in birds. Both melanic granules and alveoli (cysts) are more probably to be interpreted as of ancestral significance. As far as is known an epiphysis is present in all vertebrates, with the exception of *Myxinoides* and *Crocodilia*. No trace of an epiphysis is said to appear even in embryos of *Crocodilia*. The *pineal eye* of certain reptiles is commonly regarded as the homologue of the pineal body of mammals. However, in the lower groups of animals the true homologue is generally a double structure, the pineal eye developing terminally on a secondary anterior evagination, the parapineal, from the base of the primary one. This secondary process is not developed in mammals In Hatteria (a New Zealand "lizard") the pineal eye comes to the surface in the middle of the head, and consists of an optic cup with a lens covered by transparent epidermal scales, forming a cornea. It is believed to function only as a light or warmth perceptive organ An additional structure, the *paraphysis*, found in certain lower forms and in the marsupialia, anterior to the pineal body, and arising similarly as an ependymal evagination, is commonly regarded as a choroid plexus, evaginated instead of being invaginated, as is usually the case in mammals. In sheep the pineal undergoes its greatest development during the first year of life, approximately fivefold.

The pineal body is attached to the posterior portion of the roof of the third ventricle by means of the *pineal stalk*. This contains the *pineal recess*, a cavity continuous with the ventricle The anterior wall of the stalk is limited basally by the *habenular commissure*, the posterior wall by the *posterior commissure*. The pineal proper thus lies underneath the posterior end of the corpus callosum and rests on the anterior pair of the corpora quadrigemina. It is a solid cone-shaped structure enveloped by a capsule of pia matter, and more or less distinctly lobed (Fig. 507). It measures in man 7 millimeters in length by 5 millimeters in transverse diameter. The mammalian pineal is perhaps rather a metamorphosed than a rudimentary organ Its size bears no relation to the size of the brain or the size of the body; it is no larger in large than in small dogs, for example, and no larger in horse than in dog; that of sheep is about the size of that of man.

pherally so that two layers can now be distinguished in the wall; an inner *nuclear* and an outer non-nuclear or *marginal* layer. Cell boundaries have meanwhile become obliterated and the entire wall is now essentially a dense syncytium. Still later the syncytium assumes a looser texture, forming the *myelospongium*, and the indifferent germinal cells
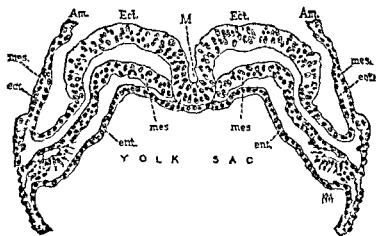
FIG 515—TRANSECTION THROUGH THE GRAF SPEE EMBRYO SHOWN IN THE PRECEDING FIGURE.

Am, amnion; *ect*, ectoderm; *mes*, mesoderm; *ent*, entoderm; *M*, neural groove (From Williams.)

give rise to two types of cells: the *neuroblasts*, from which differentiate the neurons, and the *spongioblasts*, from which the neuroglia cells and fibers develop.

Shortly after the time when neuroblasts and spongioblasts first become distinguishable the wall of the neural tube can be conveniently divided into three zones: (1) the
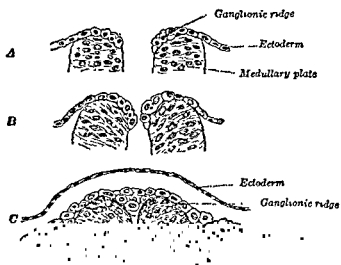
FIG 516.—THREE SUCCESSIVE STAGES IN THE PROCESS OF CLOSURE OF THE MEDULLARY (NEURAL) GROOVE TO FORM THE MEDULLARY (NEURAL) CANAL AND NEURAL (GANGLIONIC) CRESTS

(From Barker, after M. von Lenhossék.)

ependymal layer, forming internally also a limiting membrane; (2) the *intermediate*, *middle*, *nuclear* or *mantle layer*, containing neuroblasts, spongioblasts and indifferent cells; and (3) the outer non-nuclear or *marginal layer*, bounded externally by an *outer limiting membrane*. A glia framework pervades the entire width of the wall.

CHAPTER XVII

THE NERVOUS SYSTEM

DEVELOPMENT

The first external evidence of the beginning of the nervous system is the appearance of a median longitudinal furrow in the dorsal (neural) ectoderm of very young embryos (about the fifteenth day in man). This is known as the *neural* or *medullary groove*. Still earlier stages, as revealed in sections, include an increase in height of the ectodermal cells
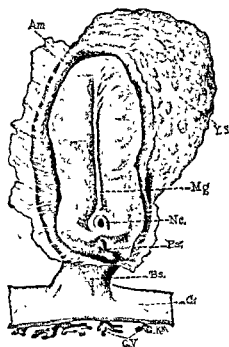
Fig 514—Human Embryo 2 Millimeters Long. (Graf Spee.) ×30

Am, amnion; *C,* chorion; *C.V,* chorionic villi; *Bs,* body stalk (embryophore); *Mg,* medullary (neural) groove; *Nc,* neurenteric canal; *Ps,* primitive streak; *Ys,* yolk sac. (From Williams)

to form an axial plate of cuboidal cells, the *neural plate.* Subsequently this simple layered plate is converted into a structure of several strata of cuboidal cells, which meanwhile forms the floor and lateral walls of the developing neural groove. The neural plate grows more rapidly laterally causing thus a progressive elevation of its borders, the *neural folds,* and producing in consequence a gradually deepening neural groove (Fig. 515). According to Glaser,[1] the inequality in growth between neural plate and the adjacent ectoderm which causes folding is due to greater water absorption on the part of the plate By continuation of this process of unequal growth medially and laterally, the folds finally meet in the dorsal midline and fuse to form the *neural tube.* On both sides of the line of fusion a group of ectodermal cells appears, the *neural* or *ganglionic crest,* from which arise the *neurons* of the dorsal and sympathetic ganglia, and the neurilemma (sheath) cells of both the afferent and efferent fibers of the dorsal and ventral roots, respectively. The neural tube (canal) is originally of approximately uniform caliber throughout; but shortly the cephalic end, by a series of processes involving dilatations, constrictions, foldings and fusions, develops into the brain; while the caudal portion gives rise to the spinal cord.

These gross developmental changes—more appropriately considered in detail in works of embryology—involve histogenetic processes in the walls of the canal. The earlier of these processes are essentially alike in both cerebral and spinal portions of the canal. Originally the ectodermal layer, which subsequently forms the wall of the tube, consists of a single layer of cuboidal cells similarly undifferentiated. Shortly spherical and oval *germinal cells* appear among the primitive *ependymal cells.* These *indifferent cells* migrate peri-

[1] Glaser, 1914

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axon proper, passes into the dorsolateral portion of the cord as an afferent fiber and here makes contact through a telodendrion either directly or indirectly (through association neurons) with the dendrons of motor neurons. Its peripheral process is to be regarded as the dendron, modified structurally so as to be essentially identical with the axon.

The sympathetic may be regarded as a cenogenetic addition to the cerebrospinal nervous system. Ontogenetically it appears in man at the beginning of the fifth week (7 millimeter embryo). Phylogenetically, it first appears in cyclostomes. Kuntz[2] traces the neurons of the sympathetic trunks and the prevertebral plexuses to neuroblasts in both the neural crest and the medullary wall, from whence they are said to migrate by both the
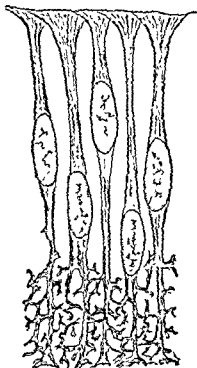
FIG. 520.

FIG. 521.

FIG. 520.—SECTION THROUGH WALL OF LATER NEURAL TUBE OF RABBIT EMBRYO, SHOWING A STAGE IN THE DIFFERENTIATION OF THE EPENDIMA CELLS AND THE FORMATION OF A MYELOSPONGIUM (His)
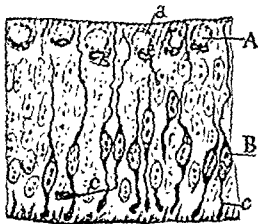
FIG 521 —SECTION OF WALL OF FOREBRAIN OF FOUR-DAY CHICK EMBRYO.

A, apolar neuroblast ; *B*, bipolar neuroblast ; *a*, the beginning of the sprouting of the axon ; *c*, axons, showing the terminally expanding growth area (cone of growth). Cajal's silver technic. (Heidenhain, after Cajal.)

dorsal and ventral nerve roots. The neurilemma cells, as also the capsular elements of the sympathetic neurons, arise from "indifferent" cells which migrate from these same locations and proliferate and differentiate along their course The cardiac plexus and the sympathetic plexuses in the walls of the visceral organs (terminal plexuses; "vagal sympathetic" plexuses—Kuntz) have their origin, according to Kuntz, in nervous elements which migrate from the hindbrain and the vagus ganglia along the fibers of the vagus nerves Kuntz believes that "indirect embryological and anatomical evidence warrants the conclusion that the sympathetic excitatory neurons arise from cells which migrate from the neural tube along fibers of the motor nerve roots, while the sympathetic sensory neurons, wherever such neurons exist. arise from cells which migrate from the cerebrospinal ganglia." However, according to Carpenter[3] the autonomic neurons show no distinct differences from the standpoint of their chromophilic content Since such differences are conspicuous between the sensory and motor

[2] Kuntz, 1910

[3] Carpenter, 1914

Neuroglia cells differentiate from spongioblasts by a process involving chiefly the formation of glia fibers in their exoplasm. These fibers apparently arise from spongioplasmic fibrils of the protoplasm. Many glia fibers subsequently become disposed extracellularly. The primitive ependymal cells become greatly modified into stout, slightly branching fibers extending through the width of the walls of the neural tube. The main body, of columnar shape, with its nucleus and a distal tuft of cilia, retains its central position and forms an ependymal lining for the spinal canal and the ventricles of the brain. The several neuroglia constituents (astrocytes, oligodendroglia and glia fibers) form a loose-meshed syncytium, the myelospongium, for the support of the developing neuroblasts. Peripherally it is of denser texture and relatively free of nuclei, and is designated the *marginal layer* (glial sheath). Coincident with this process of neuroglia histogenesis, the neuroblasts enlarge, proliferate extensively and differentiate into neurons, their processes—axon and dendrons—arising as sprouts from the originally spherical neuroblasts. Subsequently microglia appears as an invasion from the pia mater. The microglia cells constitute the macrophages of the central nervous system.

FIG 517.—CELL LINING THE NEURAL CANAL OF THE NEWLY HATCHED RAINBOW TROUT, SHOWING MITOCHONDRIA IN AN EMBRYONIC NERVE CELL.

Meves' technic. × 2000

The motor neurons remain located in the ventral horn of the spinal cord (Fig. 524), their axons (efferent fibers) passing out through the ventral root to unite with the fibers of the dorsal root to form a spinal nerve. The sensory neurons arise external to the cord from neuroblasts of the linear neural crests, and migrate some distance ventrolaterally, where they aggregate into metameric oval masses which differentiate into the spinal ganglia. The differentiation process includes both capsule and neuron formation. The sensory neuron located in the dorsal (spinal) ganglia is also originally spherical or oval; subsequently it becomes bi-

FIG 518.   FIG 519.

FIG 518.—SECTION THROUGH NEURAL PLATE OF A RABBIT EMBRYO. The cells include a large round germinal cell. (After His.)

FIG. 519—SECTION THROUGH NEURAL PLATE OF CLOSING NEURAL GROOVE OF RABBIT EMBRYO. Two germinal cells are visible. (His.)

polar; and finally, by a process involving the retraction of the cell body (cyton) from its two processes and the fusion of these processes proximally, it becomes a unipolar cell. The definitive axon thus divides in the manner of a T or Y. Its central process, or

THE SPINAL CORD

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neurons of the cerebrospinal system, this observation arouses skepticism regarding the presence of sensory sympathetic ganglion cells.

The primary cerebral divisions and their major adult derivatives are enumerated in the appended outline (page 542). The microscopic anatomy of their definitive condition lies outside the scope of this book. These matters are more appropriately treated in special textbooks of Neurology (e.g., Quain, *Anatomy*, Vol. III, 1908; Villiger, *Brain and Spinal Cord*, translation by Piersol, 1912; and Ranson, *The Anatomy of the Nervous System*), and constitute the work of a separate course. Likewise the developmental history is more advantageously considered in a special course in embryology.

This work will include only the histology of the several segments of the spinal cord; and that of the cerebellar and cerebral cortex.
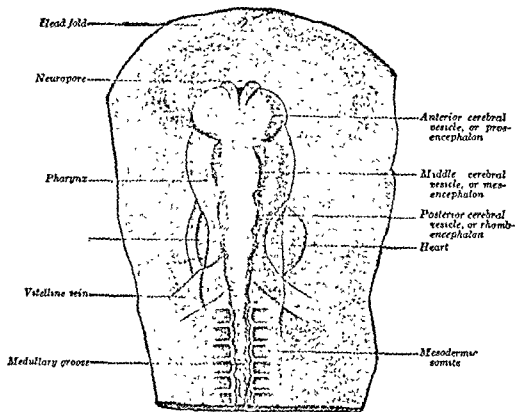
FIG. 525—RECONSTRUCTION OF THE ANTERIOR PORTION OF THE BODY OF A YOUNG CHICK EMBRYO, SEEN FROM THE DORSAL SURFACE (Kollmann)

THE SPINAL CORD

STRUCTURE

The spinal cord (Fig. 526) consists of a considerable mass of central gray matter which is surrounded by a layer of myelinated nerve fibers, the white matter.

The gray matter comprises two lateral portions united by a central commissure (*gray commissure*) in transverse section resembling the letter H. Each lateral portion includes a ventral and a dorsal *horn* with an intervening deeper portion, the central mass or *intermediate zone* of Golgi. Each horn or *cornu* ends in a head or *caput* united with the intermediate portion or *basis cornu* by a neck or *cervix cornu*.
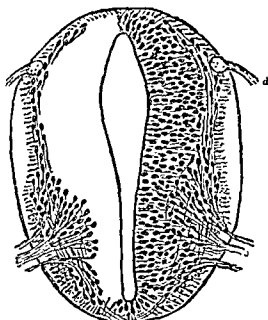
FIG. 522   FIG. 523

FIG. 522.—TRANSECTION OF THE SPINAL CORD OF AN EARLY EMBRYO, SHOWING THE MIGRATION
OF NEUROBLASTS TOWARD THE MARGINAL VEIL, AND THE VENTRAL NERVE ROOT.
a, neural canal; *b*, ventral root. (His.)

FIG. 523.—TRANSECTION OF THE SPINAL CORD OF A HUMAN EMBRYO OF FOUR WEEKS.
The central canal is immediately surrounded by ependyma cells. The peripheral nerve cells
are shown on the left of the figure. The ventral nerve roots are already pushing outward from
the primitive cord. *d*, dorsal; *v*, ventral nerve roots. (His.)
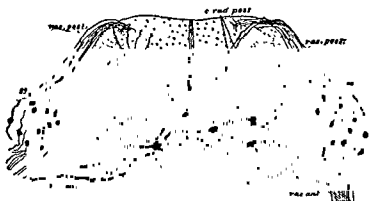
FIG. 524.—TRANSECTION OF THE SPINAL CORD OF AN EMBRYO CHICK.
c rad. ant., axons to the ventral roots; *c, rad post.*, axons to the dorsal roots; *col.*, collateral
from an axon back to the gray matter; *gg*, dorsal root ganglion; *rac. ant*, ventral root; *rac.
post*, dorsal root. (van Gehuchten.)

immediate vicinity, but also include many processes which come from very distant regions. The gray reticulum is thus supplied from fibers of the ventral and dorsal nerve roots, together with innumerable collaterals, not only from the root fibers, but more especially from those fibers which collectively form the many large tracts passing up and down the spinal cord and placing each segment in communication with many other levels of both the spinal cord and brain.

The center of the gray commissure contains the *central canal* which lies in the axis of the spinal cord and is continuous above with the ventricles of the
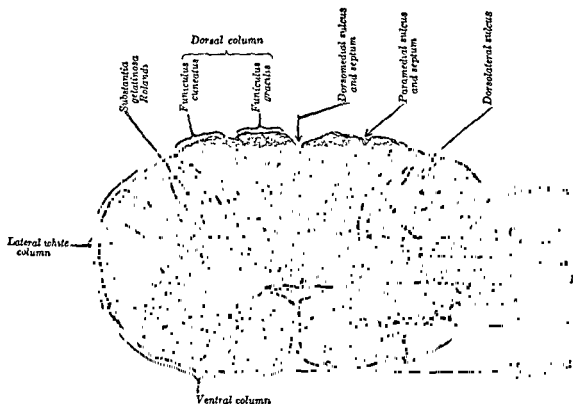
FIG. 526.—TRANSECTION OF THE SPINAL CORD OF A CHILD, SEVENTH CERVICAL SEGMENT.
Weigert stain. ×7.

brain. It represents the remains of the fetal neural canal; and in the young subject is still patent, filled with cerebrospinal fluid, and lined by columnar cells which are frequently ciliated. In older subjects the cells of the lining epithelium have usually lost their cilia, and the lumen of the canal is more or less filled by cell proliferation which involves not only the lining epithelium but also the surrounding glia cells. The central canal is immediately surrounded by a peculiar gelatinous tissue in which are many glia cells. This mass is called the *substantia gelatinosa centralis*. A similar area of gelatinous tissue occurs near the extremity of the dorsal horns, and is called the *substantia gelatinosa Rolandi*. The latter, the substantia gelatinosa Rolandi, however, is said to contain only a scanty supply of neuroglia.

DERIVATIVES OF THE NEURAL TUBE

NEURAL CANAL			
A. Myelon (spinal cord)			1. Sacral region 2. Lumbar region 3. Thoracic (dorsal) region 4. Cervical region
B. Encephalon (brain)	I. Rhombencephalon (rhomboid brain)	(a) Myelencephalon (afterbrain)	5. Medulla oblongata
		(b) Metencephalon (hindbrain)	6. Pons varolii 7. Cerebellum
	II. Mesencephalon (midbrain)	(c) Mesencephalon (midbrain)	8. Region of the crura cerebri (brain stem); corpora quadrigemina
	III. Prosencephalon (forebrain)	(d) Diencephalon (interbrain or 'tween brain)	9. Region of the optic thalami (basal nuclei) 10. Optic tract (primitive optic evaginations) 11. Posterior lobe of hypophysis cerebri 12. Pineal body
		(e) Telencephalon (endbrain)	13. Cerebral cortex (pallium) 14. Corpora striata 15. Olfactory lobes

The ventral is somewhat broader than the dorsal horn. Its cells supply axons, which, after uniting into bundles, pass ventralward through the white matter to form the ventral (anterior) *nerve roots.*

The spinal cord may be considered as consisting of ontogenetic *segments* whose number corresponds to the number of the spinal nerves. Hence each segment contains the ventral horn cells whose axons form the ventral root of the corresponding spinal nerve.

In a similar manner the dorsal horns of the gray matter receive a large portion of the incoming fibers of the dorsal roots, which in large part form end brushes around the cells of the dorsal horns and the intermediate zone as shown in Figure 527.

The dorsal roots enter through a distinct longitudinal groove, the dorsolateral sulcus. At the exit of the ventral roots there is, however, only a broad, shallow indentation, these roots making their exit in isolated bundles distributed through a vertical plane of considerable width. The dorsal root fibers of each segment, on the other hand, enter in a single compact mass.

Gray Matter.—The gray matter consists of a dense tangle of nerve cells and unmyelinated fibers, both axons and dendrons, together with neuroglia and blood vessels. The fibers of a given area are derived not only from nerve cells in their

rounded, except at the gray commissure, by the white matter. The latter is sub-divided into a ventral, lateral, and dorsal column, each of which extends the entire length of the spinal cord and is apparently (to the naked eye only) continuous above with a similar column in the medulla oblongata.

The *ventral white column* is included between the ventral median sulcus and the ventral gray horns and nerve roots; the *lateral columns* extend from the ventral roots in front, around the lateral surface of the spinal cord, to the dorsal roots; the *dorsal columns* are included between the dorsal horns of gray matter and dorsal nerve roots, and the dorsal median septum.

Each of these columns of white matter is again subdivided by neurogliar septa of variable size and number, which extend inward from the pia mater for a considerable distance. Such septa may even penetrate all the way to the central gray matter. One of these septa, the *paramedian septum*, more constant than the others, subdivides the dorsal column into two portions, a *dorsomedial* and a *dorsolateral column*, or the *funiculus gracilis* (column of Goll) and the *funiculus cuneatus* (column of Burdach) of the upper portions of the cord.

In the ventral white column two chief *fiber tracts* are recognized: a narrow median, the *anterior* or *direct pyramidal tract*; and a more lateral larger *anterior ground bundle*. In the lateral column four main tracts are recognized: three lateral, including an upper *crossed pyramidal tract*, a middle *direct cerebellar tract*, and a lower *Gower's column*; and a large medial *lateral ground bundle* (Fig. 527) These tracts do not possess sharp boundaries. Moreover, the ground bundles at least are composite. The several elementary tracts contain fibers passing either from the periphery to the brain along the cord (*ascending fibers*) or from the brain through the cord to the periphery (*descending fibers*), or fibers connecting brain and cord or different segments of the cord. For a detailed description of the constitution of these fiber tracts reference must be made to the systematic textbooks on the nervous system.

The larger blood vessels are distributed along the fibrous septa, taking their origin from the vessels of the pia mater; the most of them are distributed to the white matter, but to some extent these larger blood vessels also supply the gray matter.

The entire surface of the spinal cord presents, just beneath the pia mater, a thin superficial layer or *marginal layer* of glia tissue. In the brain this layer is somewhat exaggerated in thickness.

The varying number of fibers which are given off at different levels of the spinal cord results in considerable differences in size in its several portions. By means of these peculiarities, as well as by the several nerve roots to which they give origin, we distinguish a sacral, lumbar, thoracic, and cervical region. Each of these regions presents certain more or less important morphological characteristics.

Sacral Region.—In the sacral region the investment of *white matter* is very thin, the gray matter—though actually less in amount than in the more cephalad regions—appearing large by comparison. Both the ventral and dorsal horns of
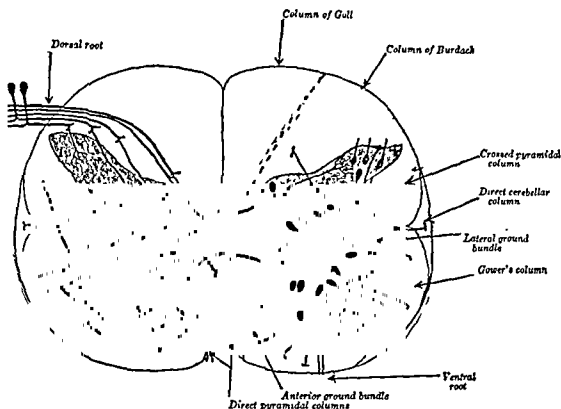
FIG. 527.—THE FIBER PATHS OF THE SPINAL CORD.

The black cells are of the sensory or centripetal paths, those on the left are spinal ganglion whose branches may be traced to their several terminations within the spinal cord. The cells of anterior horn on the right are white; commissural cells are vertically striped; small cells of the dorsal horns are horizontally striped; a small Golgi cell of the dorsal horn stippled. (Redrawn after the scheme of von Lenhossék.)

White Matter.—The white matter forms a covering or shell around the central mass. It increases in thickness from below upward. This peculiarity is the result of the progressive influx of centripetal fibers, and a corresponding contribution of centrifugal fibers, through the spinal nerves of each successive segment. The dorsal median *septum* extends inward from the shallow sulcus on the dorsal surface of the spinal cord to the central gray commissure, and divides the dorsal mass of white matter into two white columns, lying on either side of the median line, and bounded laterally by the dorsal horns of gray matter and the dorsal nerve roots. The ventral median *sulcus* in a similar manner, splits the ventral portion of white matter into the two ventral white columns. This sulcus, however, does not penetrate all the way to the gray commissure but leaves an interval of white matter containing many transverse and obliquely disposed nerve fibers. The ventral or *white commissure* thus formed connects the two ventral columns of white matter.

The spinal cord is thus divided into two lateral and symmetrical halves by a plane passing through the ventral and dorsal median sulci and the central canal. Each lateral half includes a central curved mass of gray matter completely sur-

the medullary canal to form the central ligament, which is finally attached to the sacrum or coccyx.

Lumbar Region.—In the lumbar region there is a distinct enlargement, chiefly involving the gray substance, which here includes the immense number of cells of the ventral horns whose "motor" fibers enter the large lumbar nerve trunks for

the supply of the lower limbs. These nerve trunks also supply to the cord a great number of centripetal or sensory fibers which enter the dorsal and, later (through secondary neurons), the lateral columns; thus both of these columns are of large size in and above the lumbar region. The *dorsomedial* column in this region attains an appreciable size, and a distinct pial septum marks its lateral boundary.

The spinal cord is now nearly circular in transection, its ventrodorsal being perhaps slightly less than its transverse diameter (10 millimeters). The gray commissure lies very near the middle of the spinal cord, and the ventral median fissure is, therefore, quite as deep as the dorsal median septum.

FIG. 529—TRANSECTION OF THE SPINAL CORD OF A CHILD, THIRD SACRAL SEGMENT. Weigert stain. ×7.

Both the ventral and dorsal gray horns are long and thick. Each dorsal horn contains a large apical area of gelatinous substance, is somewhat longer on its lateral than on its medial side, and reaches nearly to the dorsal surface of the spinal cord, opposite the dorsolateral sulcus. The dorsal nerve roots entering at this level are *apparently* directed toward the middle of the tips of the dorsal horns of gray matter; once within the spinal cord they pass around to the mesial side of the dorsal horns.

The ventral horns, somewhat larger than the dorsal, present two short and broad protuberances, the one at the ventromesial, and the other and more prominent at the ventrolateral angle A similar though less prominent protuberance is seen at the base of the ventral horn, on its lateral aspect. Each of these projections contains a more or less well-defined group of motor nerve cells. The cell groups of the ventral horns in the lumbar region are therefore a *ventromedial, ventrolateral,* and *dorsolateral,* together with an ill-defined central group occupying the deeper intermediate zone of gray matter.

FIG 530—TRANSECTION OF THE SPINAL CORD OF A CHILD, FIFTH LUMBAR SEGMENT. Weigert stain ×7.

The nerve centers contained in the lumbar region control the reflexes and musculature of the lower limbs and also those of the lower part of the abdominal wall.

gray matter are short and thick. The substantia gelatinosa Rolandi is of considerable volume. The cell groups in the ventral horns of this region are a *ventromedial* and a *dorsolateral*.

The cord as a whole is small and its transection nearly circular in outline. The five segments of this region contain the neuron centers for the urinary bladder,

FIG 528—VARIETIES OF NEUROGLIA IN SPINAL CORD OF CHILD.

A, ependymal cells lining central canal; B, long-rayed (spider) cells of white matter; C, short-rayed (mossy) cells of gray matter; D, long-rayed astrocytes of gray matter. Golgi technic (Cajal.)

the anus, some of the musculature of the lower limbs, and the sensory reflexes of the perineum and genito-urinary organs.

Below the sacral region the spinal cord tapers rapidly (*conus medullaris*) and is continued downward for a considerable distance as the *filum terminale*. The surrounding leash of lumbar and sacral nerve roots forms the *cauda equina*. The fibrous membranes which surround the cord continue even farther downward in

posterior. The major portion of the white matter is still contained within its dorsal rather than its ventral portion, the gray commissure appearing to lie somewhat ventral of the center. The dorsal median septum dips inward for a much greater distance than does the ventral median fissure

The dorsal columns are decidedly larger than the ventral, and a distinct groove, the paramedian sulcus, from which a fibrous septum is continued inward, separates the dorsomedial from the dorsolateral column.

The dorsal gray horns are long, relatively slender, and more divergent than in the lower levels. They do not reach the surface of the spinal cord, but are connected therewith by the long, slender dorsal nerve roots. The gray matter of the dorsal horns in this region is more or less invaded by bundles of nerve fibers derived from the lateral and dorsal columns; the tips of the dorsal horns are thus almost cut off from the deeper portions of gray matter.

FIG. 532—TRANSECTION OF THE SPINAL CORD OF A CHILD, FOURTH CERVICAL SEGMENT.
Weigert stain. ×7.

The ventral horns are both long and broad. They present three noticeable promontories or processes—a medial (ventromedial), a ventral (ventrolateral), and a lateral. The lateral, because of its special prominence, is frequently called the *lateral horn*; it is one of the noticeable characteristics of the cervical region.

Each of these processes contains a corresponding cell group; hence we distinguish in the cervical enlargement a *mesial*, a *ventral*, and a *lateral* group, together with a small *intermediolateral*, which is partially or completely detached from the dorsal portion of the lateral group There is also a small disseminated *central group* of nerve cells occupying the deeper portion of the ventral horn.

The nuclei of the segments included in the cervical enlargement contain the centers for the musculature and sensory reflexes of the upper limbs. The partial control of the pupillary movements in the eye is also located in the lowermost segments of this region.

Upper Half.—In the upper half of the cervical region a transection of the spinal cord, except for its larger size, resembles very closely that of the thoracic

Thoracic Region.—A transection of the spinal cord in the thoracic region is of small diameter (8 millimeters), and is very nearly circular in outline. The white matter, *since it contains the many nerve fibers going to and coming from the lumbar enlargement, is much more voluminous than the gray matter.* The latter is reduced to a comparatively small central mass.

The dorsomedial column attains a considerable size in this region, and is distinctly marked off from the adjacent dorsolateral column by a fibrous septum derived in part from the pia mater, in part being of neuroglia composition. The dorsal and the lateral columns, *having been much augmented by the influx of fibers from the large dorsal roots of the lumbar nerves,* form the larger part of the white matter. The gray matter consequently appears to be pushed forward, its gray commissure lies considerably ventrad of the center of the spinal cord, the ventral median fissure *is shorter than the dorsal median septum,* and the tips of the dorsal gray horns are far removed from the surface, being only connected with the dorsolateral sulcus by the slender dorsal nerve roots. In fact, the dorsal horns of gray matter *in this region* are reduced to a minimum size; they are short and slender and contain comparatively few nerve cells.

FIG. 531.—TRANSECTION OF THE SPINAL CORD OF A CHILD, EIGHTH THORACIC SEGMENT.

Weigert stain. ×7.

At the base of each dorsal horn, on its mesial side, there is a distinctly outlined cell group whose transection is of oval or circular outline. Indeed, this cell group, the *cell column of Clarke,* begins in the second or third lumbar segment, and is continued upward to the second or third thoracic—at times even into the lowermost cervical segments—at which level it has dwindled to a relatively insignificant group. In the lower lumbar region an ill-defined group of cells occupying *a similar position and having the same* function is known as the *nucleus of Stilling.*

The ventral gray horns are very short and narrow, and their cells cannot be subdivided *into groups as in the other regions of the spinal cord.* In the upper part of the thoracic region a distinct protuberance makes its appearance at the base of the ventral horn, on its lateral aspect. This is the precursor of the larger *lateral horn* of the cervical region. In the upper thoracic region it contains a small cell group, the dorsolateral.

The nerve centers of the thoracic segments control the upper abdominal region, the thorax, and the viscera.

Cervical Region.—*Lower Half.*—In the lower half of the cervical region the spinal cord presents a distinct enlargement, within the gray matter of which are the nuclei for the upper limbs. The spinal cord in this region is somewhat flattened, its transverse diameter (14 millimeters) considerably exceeding *its antero-*

posterior. The major portion of the white matter is still contained within its dorsal rather than its ventral portion, the gray commissure appearing to lie somewhat ventral of the center. The dorsal median septum dips inward for a much greater distance than does the ventral median fissure.

The dorsal columns are decidedly larger than the ventral, and a distinct groove, the paramedial sulcus, from which a fibrous septum is continued inward, separates the dorsomedial from the dorsolateral column.

The dorsal gray horns are long, relatively slender, and more divergent than in the lower levels. They do not reach the surface of the spinal cord, but are connected therewith by the long, slender dorsal nerve roots. The gray matter of the dorsal horns in this region is more or less invaded by bundles of nerve fibers derived from the lateral and dorsal columns; the tips of the dorsal horns are thus almost cut off from the deeper portions of gray matter.

FIG. 532.—TRANSECTION OF THE SPINAL CORD OF A CHILD, FOURTH CERVICAL SEGMENT.
Weigert stain. ×7.

The ventral horns are both long and broad. They present three noticeable promontories or processes—a medial (ventromedial), a ventral (ventrolateral), and a lateral. The lateral, because of its special prominence, is frequently called the *lateral horn;* it is one of the noticeable characteristics of the cervical region.

Each of these processes contains a corresponding cell group; hence we distinguish in the cervical enlargement a *mesial,* a *ventral,* and a *lateral* group, together with a small *intermediolateral,* which is partially or completely detached from the dorsal portion of the lateral group. There is also a small disseminated *central group* of nerve cells occupying the deeper portion of the ventral horn.

The nuclei of the segments included in the cervical enlargement contain the centers for the musculature and sensory reflexes of the upper limbs. The partial control of the pupillary movements in the eye is also located in the lowermost segments of this region.

Upper Half.—In the upper half of the cervical region a transection of the spinal cord, except for its larger size, resembles very closely that of the thoracic

Corpora qu·
Velum med
anterit
Vent. quart

Vr:··
A···1.··13
Corpus medull. cerebelli
Medulla oblongata

Fissura transversa cerebri
Aqueductus cerebri

Tela chorioidea ventriculi tertii
Corpus pineale

Ventriculus tertius   Massa intermedia

Foramen interventriculare (Monroi)
Columna fornicis
Septum pellucidum
Lamina rostralis

Commissura anterior
Lamina terminalis
Chiasma opticum
Infundibulum   Hypophysis

Tuber cinereum
Corpus mammillare
Pons (Varolia)

FIG. 533.—MEDIAN SAGITTAL SECTION THROUGH THE BRAIN. (Toldt.)

550

region. The larger size is due to an increase in the white matter of the dorsal and lateral columns, consequent upon the acquisition of new fibers which enter the subjacent segments from the nerves supplying the upper extremities, together with an increased number of centrifugal fibers from the cerebrum which are distributed to the gray matter of this region.

The ventral columns are also much increased in size by the addition of many fibers coming down from the medulla and cerebellum, which place the nerve centers of the spinal cord in close relation with those of the cranial nerves and with the association centers of the cerebellum.

In addition to the large size of its white columns, a noticeable characteristic of the upper cervical region is the prominence of its lateral horns of gray matter. Just dorsal to the lateral horns is also a peculiar *reticular formation* which results from an invasion of the adjacent portions of the lateral white columns by bands of gray matter. The gray matter thus forms a coarse network whose meshes inclose isolated bundles of longitudinal fibers.

The ventral horn cells of this region are scarcely divisible into groups, but a large and distinct cell group, the *intermediolateral cell column*, occupies the so-called lateral horn.

The nuclei of the upper cervical region innervate the skin and muscles of the neck and shoulder, they also supply the diaphragm. The nerve cells of this region not only supply the cervical spinal nerves, but they also send root bundles to the spinal accessory or eleventh cerebral nerve.

THE CEREBELLUM

The cerebellum consists of an irregular core of white substance, the *medulla*, and a thick mantle of gray matter, the *cortex*. It comprises two hemispheres or lobes connected by a third lobe, the *vermis*. Each lobe is a combination of lobules which include a variable number of transverse convolutions or *folia* Each folium contains a medullary core and is covered by a cortical layer. The central medulla contains four paired masses of gray substance, the *internal nuclei*.

THE CEREBELLAR CORTEX

The *cortex* is divisible into an inner *granular layer,* and an outer *molecular layer.* The granular layer in a fresh section appears rust-colored; in a stained preparation it appears much darker and more granular than the molecular layer due to the abundance of nuclei; it is thickest over the summit of the folium, and thinnest in the depth of the sulcus between adjacent folia.

Purkinje Cells.—The most conspicuous and distinctive elements of the cerebellar cortex are the Purkinje cells, situated along a line marking the division between molecular and granular layers They are regarded as belonging to the molecular layer. The remaining cellular elements of the cortex cannot be studied in detail in ordinary histologic preparations. They must be identified mainly by their relative size and position. Our knowledge of their finer structure and their

Laminai rostralis
Septum pellucidum
Columna fornicis
Foramen interventriculare (Monroi)
Massa intermedia
Ventriculus tertius
Tela chorioidea ventriculi tertii
Corpus pineale
Fissura transversa cerebri
Aquaeductus cerebri (Sylvii)
Corpora quadrigemina
Velum medullare anterius
Vent. quart.

Ven...
Arbor vitæ
Corpus medull. cerebelli
Medulla oblongata

Commissura anterior
Lamina terminalis
Chiasma opticum
Infundibulum
Hypophysis
Tuber cinereum
Corpus mammillare
Pons (Varolii)

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550

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interrelationships has been gained by use of special staining technics, chiefly the Golgi process. By use of this technic two other types of cells can be distinguished in the molecular layer: the *small cortical cells*, and the large cortical or *basket cells*.

The Purkinje cells are large flask-shaped elements, with typically a robust dendron and a delicate axon at opposite poles. The axon passes centrally to con-

FIG. 534.—VERTICAL SECTION OF FOLIUM OF HUMAN CEREBELLUM, SHOWING SUPERFICIAL MOLECULAR LAYER, CENTRAL GRANULAR LAYER, AND THE INTERVENING LAYER OF PURKINJE CELLS. ×70.

tribute to the white matter of the medulla. It gives off numerous collaterals, some of which turn back into the molecular layer and terminate in relation with neighboring cells of Purkinje. The dendron passes toward the surface dividing almost

immediately into two coarse branches, which each divides dichotomously into a succession of increasingly more delicate branches forming peripherally a dendronic field of extreme profusion of nonanastomosing fibrils. The dendron viewed as a whole constitutes a fan-shaped structure. Its expansion is in a plane at right angles to the long axis of the convolution. In sections parallel with the long axis of the convolution the dendronic field is very narrow, and never wider than the diameter of the cell body.
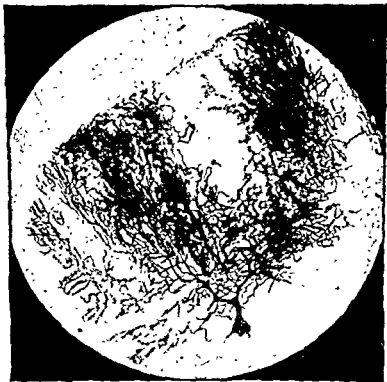
Fig. 535.—A Purkinje Cell from the Human Cerebellar Cortex. Moderately magnified. Photo. (Berkley.)

Basket Cells.—The basket cells, or *large cortical cells*, are multipolar elements with relatively short robust branching dendrons, and a long axon which passes horizontally in the same plane in which the dendronic expansion of the Purkinje cells are placed. Along its course it gives off five or six collaterals which, as also the postcollateral portion of the axon itself, pass centrally toward the Purkinje cells where each breaks up into a profuse terminal arborization which invests the cell body in the manner of a "basket." The basket cells occupy the middle and .outer portions of the molecular layer; these basket cells are apparently of the nature of association neurons, perhaps coördinating the function of a number of Purkinje cells.

Small Cortical Cells.—The small cortical cells are distributed throughout the molecular layer but are more abundant in the outer half. They are multipolar and vary considerably in size, some being almost as large as the basket cells. They possess from two to five delicate dendrons distributed for the most part in the

same plane as those of the Purkinje cells. Their short slender axon, which is horizontally placed, is frequently characteristically looped. The axon of some of these cells has numerous collaterals.
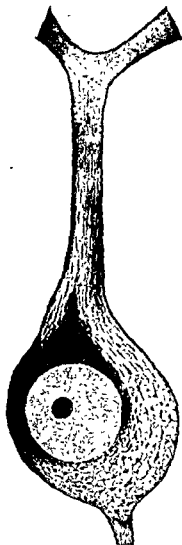
FIG 536.—A PURKINJE CELL FROM THE CEREBELLAR CORTEX OF THE RABBIT
Highly magnified. (Nissl.)

Nuclear or Granular Layer.—The nuclear or granular layer also contains three distinct types of cells: the *granule cells*, the *large stellate cells* and the so-called *solitary cells*. The latter are small fusiform elements, but of their significance and relationships little is definitely known.

Granule Cells.—The granule cells have a general distribution throughout the granular layer. They are of relatively small size, multipolar, and possess short dendrons (frequently four) which end in claw-like processes. These latter are *in close relationship with* the so-called *eosin bodies*, small spheroidal finely granular masses having a special affinity for eosin. The eosin bodies are believed by some to represent synapses between the dendrons of, the granular cells and the telodendria of the centripetal mossy fibers contributed by the medulla. The axon of the granule cell is unique among the cerebellar cortical neurons in that it passes toward the surface; here it divides in T-fashion, the branches passing *parallel to the long axis of the con*volutions thus coursing at right angles to the dendronic expansion of the Purkinje cells, in relation with which they probably end.

Large Stellate Cells.—The large stellate cells have a limited distribution in the granular layer; they are more or less closely confined to the boundary zone between the molecular and granular layers. They are large multipolar cells, with a profuse dendronic contribution to the molecular layer, and an almost equally profuse short axonic and collateral contribution to the granular layer where the telodendria end *in relation to* the granule cells. These are typical Golgi cells of the second type.

THE MEDULLA

The medulla next the cortex contain three important types of *myelinated* fibers: the climbing fibers, the mossy fibers, and the axons of the Purkinje cells. The latter are centrifugal fibers passing to the internal nuclei. The *climbing fibers* are so designated by reason of their ending in profuse telodendria which are closely associated with the dendrons of the Purkinje cells, apparently climbing over them. The *mossy fibers* owe their designation to the nodular mossy char-
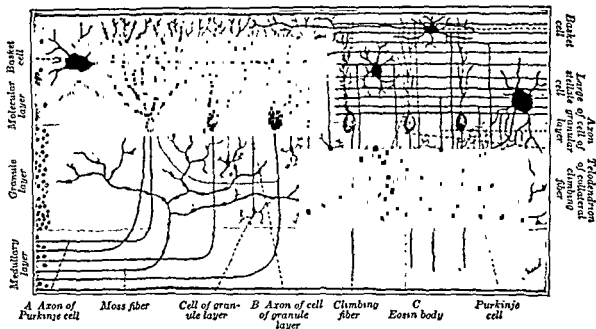
FIG. 537—DIAGRAM OF THE CEREBELLAR CORTEX.

A, by ordinary nuclear staining (omitting the layer of the Purkinje cells); *B*, vertical to the surface of the convolution; *C*, longitudinal section through the convolution; *B* and *C*, by the chrome-silver method (slightly modified from Böhm and Davidoff)

acter of their terminal branches within the granular layer. Their end-arborizations are intimately related to those of the dendrons of the granule cells probably contributing to the formation of the eosin bodies.

Both cortex and medulla contain an abundant neuroglial supporting substance. The astrocytes of the cortex are largely of the short-rayed (mossy) type; those of the medulla are exclusively of the long-rayed type. Next the surface of the cortex the neuroglia tissue is condensed, forming a thick peripheral velum.

The foregoing is summarized in the following outline:

Cerebellum { Lobes Lobules Folia } { Hemispheres Vermis }

I. Cortex

    A. Molecular layer

        1. Small cortical cells

        2. Basket cells; small stellate cells; large cortical cells

        3. Purkinje cells

    B. Nuclear or granular layer

        1. Granule cells, with dendronic arborizations ending in close association with eosin bodies

        2. Large stellate cells

        3. Solitary cells

II. Medulla—myelinated nerve fibers

        1. Axon of Purkinje cells

        2. Mossy fibers, ending in eosin bodies of granular layer

        3. Climbing fibers

THE CEREBRAL CORTEX

The cerebrum consists of two large symmetrically paired lobes or *hemispheres* nected by a bridge of white matter, the *corpus callosum*. Each hemisphere ludes essentially a central mass of white substance or *medulla*, containing the rnal nuclei or *basal ganglia*—paired masses of gray matter—and a covering gray substance, the cortex or *pallium*. The cortex is greatly folded, thus oming marked by convolutions or *gyri* with intervening fissures or *sulci*. The face of each hemisphere may be divided into four principal lobes: (1) the ntal lobe, bounded posteriorly by the fissures of Rolando and Sylvius; (2) the
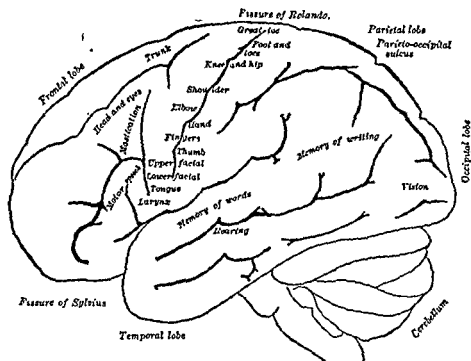
538.—Left Lateral Surface View of Cerebral Cortex in Man, Showing the Lobes, Main Sulci and the Larger Functional Areas.

Later researches have shown that the motor area is located entirely in the preclandic region openheim)

ietal lobe, extending from the fissure of Rolando in front to the parieto-ipital fissure behind and the sylvian fissure below; (3) the *occipital lobe*, nded anteriorly by the parieto-occipital sulcus; and (4) the *temporal lobe*, g below the fissure of Sylvius. The cortical portion folded under the lips of sylvian fissures is known as the *insula* (lobulus insulae). The average thickness the cortex is about three millimeters, but in the motor area of the frontal lobe, nay attain a depth of five millimeters, while in the occipital lobe it may become uced to almost two millimeters.

The nerve cells which enter into the formation of the gray matter of the ebral cortex present a remarkable tendency to arrange themselves in more or

THE CEREBRAL CORTEX 557

less well-defined layers parallel to the surface of the cerebral convolutions. The number and arrangement of these layers in the various lobes varies, however, with the peculiar function of each of these areas. Thus, in the motor area there is a five layer type, in the parietal lobe a seven layer type, in the occipital lobe a six or eight layer type. The histologically different areas shade into each other by insensible gradations.

In general, it may be assumed that the nerve cells of all of these layers are included in one or two physiologically distinct groups or types; those whose axons enter the projection paths, and those whose axons enter the association paths; also that while these cells intermingle with each other in all portions of the cortex, yet certain areas are characterized by an undue proportion of one or the other type, and may accordingly be considered as either projection centers or association centers.

The larger cells belong, as a rule, to the projection centers, and the peculiar type of large cell contained in a given center may often be considered as characteristic of that particular area. Thus the motor area contains giant pyramidal cells (Betz cells), and the visual area the giant "solitary cells" of Meynert.

The larger cells, being of Golgi's Type I, are assumed to be connected with the projection fibers. On the other hand, the smaller cells—granule cells, polymorphous

FIG. 539—LARGE PYRAMIDAL CELL OF THE CORTEX

The Nervous System (From Barker, after W von Bechterew.)

cells, etc.—which more frequently belong to Golgi's Type II, are thought to supply the axons of association paths. Those large areas—parietal lobe, frontal lobe, lobulus insulae—which consist in so large a part of the smaller type of cells, may therefore be supposed to contain the larger association centers

The cells in any given portion of the cortex are not only arranged in layers parallel to the surface of the cerebral convolutions, but the passage of fibers of the medulla to or from their terminations within the pallium, also separates the cells of the cortex into irregular rows or striations, whose axis is perpendicular to the surface of the convolutions.

FIG. 540.—SCHEME OF THE MOTOR AREA OF THE CEREBRAL CORTEX, SHOWING THE EFFECT OF VARIOUS STAINING METHODS

1, Golgi's stain, 2, Weigert's stain, 3, hematein and eosin; 4, relative depth of each layer. A, association neurons, Ag, angular cells of the polymorphous layer; As F, association fibers, Ax, axons; C, collaterals; C F, centripetal fibers, E, terminal fibers, F, fusiform cell of the polymorphous layer; G, Golgi cells, Type II, M, cells of Martinotti; P C, collateral of a pyramidal cell; Py, pyramidal cells; Py ax, axon of a pyramidal cell; Py S, pyramidal axons passing to the cerebral medulla. (Berkley.)

THE MOTOR AREA

In the motor area, including the prerolandic or precentral gyrus and a posterior portion of the frontal lobe, the cortical cells form five tangential layers, as follows: molecular layer, outer polymorphous cell layer, small pyramidal cell layer, large pyramidal cell layer and inner polymorphous cell layer.

Molecular Layer.—The molecular layer (stratum zonale) consists of a network of fine dendronic fibers, derived from the deeper layers, which are disposed in tangential meshes beneath the pia mater. Occasionally small cells, apparently displaced from the deeper cell layers, are scattered among these fibers; they are of polymorphous form, and their processes are confined to the molecular layer. The surface of the molecular layer is covered by a *marginal velum* of neuroglia homologous with that beneath the pia mater of the spinal cord.

Outer Polymorphous Cell Layer.—The second, or outer polymorphous, cell layer, is a thin stratum. Its cells are frequently clumped, thus forming groups of various size. This grouping is, however, more distinct in some other regions, e g., the olfactory area, than in the motor area itself.

Small Pyramidal Cell Layer.—The third layer, small pyramidal cells, is somewhat thicker than the above. It consists of numerous small cells—triangular, pyramidal or pyriform in shape—whose pointed apices are directed toward the surface. Three sets of dendrons are given off by these cells, an apical process which passes outward to ramify in the outer molecular layer, and from either side of the base of the cell a second set, whose processes are distributed in a plane nearly corresponding to that in which their cell bodies lie. The axon is usually given off from the basal surface of the cell, and passes from this point directly inward to the white matter of the cerebral medulla.

Large Pyramidal Cell Layer.—The fourth layer, that of the large pyramidal cells, is also a thick layer. Its cells are of the same shape, and distribute their processes after the same manner as those of the small pyramidal cell layer. The motor area is specially characterized by the large size of the cells of this layer. The largest of these, the *cells of Betz*, are about six times as large as the small pyramidal cells, which have a fairly uniform size of about ten microns.

Inner Polymorphous Cell Layer.—The fifth, or inner polymorphous cell layer, is thicker than the preceding. Its cells are of very varied form—pyramidal, stellate, fusiform and granule cells—and are less densely packed than is the case in the more superficial layers. They are intermediate in size, between the cells of the second and the third layers. The axons of the inner polymorphic cells, in large part, pass to the white matter of the medulla, though some of them are distributed laterally to neighboring convolutions. Their dendrons are partially distributed within the layer in which they arise, but by far the larger portion pass to the more superficial pyramidal cell layers. Many of the nerve cells of this layer, e.g., the *granule cells*, are very small, their nucleus being covered with an extremely narrow shell of cytoplasm.

It is noticeable that, as a rule, the dendronic processes from the cells of all

five layers are distributed either in the same plane as their cell bodies, or they pass toward the surface, where many of them enter the superficial *molecular* layer. The axons, on the other hand, are directed inward toward the white matter of the cerebral medulla, in which they pass, either as association or as projection fibers, to many very distant parts. Notable exceptions to this latter rule, however, are the so-called *cells of Martinotti*, which occur to some extent in all layers, but which, though found in the pyramidal layers, are especially numerous among the polymorphous and granule cells. They are small polymorphic cells, which send their axons to the superficial molecular layer, giving off collaterals on their way. The small pyramidal cell layer is regarded as generally associative in function. The large pyramidal cells of Betz are motor; the cells of the granular layer are sensory elements. The polymorphous cell layer is thought to preside over lower cortical functions, such as those which are concerned in securing food, satisfying sexual instinct, etc.

FIG 541.— DISPOSITION OF THE NERVE FIBERS IN THE CEREBRAL CORTEX OF MAN

Between the vertical bands of *radial fibers* are the areas of *interradial feltwork. The supraradial feltwork* includes the tangential fiber layer or *stratum zonale* (*M.P.*), and the stripe of Bechterew (*Subm.P.*), c z, subpial neurogliar layer; *Gt P.P.*, outer stripe of Baillarger; *Pol.P.*, inner stripe of Baillarger, *W*, white matter. (From Barker, after L. Andriezen.)

The later histologic researches of Campbell (1905) and of Brodman (1906), and the experiments of Cushing (1909) and of Sherrington have shown that in the adult mammalian and human brain the psychomotor (Betz cell) area is entirely prerolandic (precentral), the area for bodily sensibility postrolandic.

The cell types in other portions of the cortex correspond closely to those of the motor area. There are, however, slight but characteristic variations which are worthy of notice.

Parietal Lobe.—The cortex of the parietal lobe (also of the *frontal, temporal,* convex surface of the *occipital* lobes, and the *insula*)— sensory area—presents a seven-layer type, the additional layers resulting from an aggregation of the granule cells into one plane, which thus divides the large pyramidal cell layer. This type, therefore, presents the following layers: molecular or tangential fiber layer, outer polymorphous cell layer, small pyramidal cell layer, outer large pyramidal cell layer, granule cell layer, inner large pyramidal cell layer and the inner polymorphous cell layer.

The distribution of this cortical type is suggestive of a close relation to the great association centers. Moreover, its most noticeable characteristics are the

abundance of its granule cells and the relative paucity of pyramidal cells, especially those of the giant pyknomorphic variety.

Visual Area.—In the visual area—median surface of the occipital lobe—the formation is described as either a six or an eight layer type. The pyramidal cell layers are reduced to extreme thinness, the giant pyramids being noticeably deficient. The stripes of Baillarger, thin layers of tangential fibers on the deeper portions of the cortex, are especially distinct. So many granule cells are scattered among those of the pyramidal type that it becomes scarcely possible to distinguish from one another the second, third, and fourth layers. When these three layers are individually considered, the type presents eight layers; if, however, they are collectively considered as one stratum, the type presents six layers. With this reservation, the following layers may be distinguished: molecular or tangential fiber layer, outer polymorphous cell layer, small pyramidal cell layer, the layer of granule and large pyramidal cells, the outer stripe of Baillarger (great pyramidal plexus); the granule cell layer, the inner stripe of Baillarger (polymorphous plexus) and inner polymorphous cell layer.

The special characteristics of the visual area are the abundance of tangential fibers, as evidenced by the prominent stripes of Baillarger, the thick fiber layer in the deeper part of the molecular stratum, the abundance of granule cells, the paucity and irregular form of the pyramidal cells, and finally the presence in the inner stripe of Baillarger and in the outer portion of the deep polymorphous cell layer of numerous large isolated multipolar cells, the giant *solitary cells of Meynert*. The outer stripe of Baillarger is especially prominent in the visual area (area striata) and is here known as the band of Vicq d'Azyr or the stripe of Gennari.

Auditory Area.—In the auditory area—temporal lobe—the seven-layer type is found. The structure in this area is apparently identical with that previously described for the seven-layer type in the parietal lobe.

Olfactory Area.—In the olfactory area—hippocampal gyrus—the cells of the outer polymorphous layer arrange themselves in groups, and the pyramidal cells become largely transformed into polymorphic and fusiform cells; these lie between the characteristic outer layer and the inner layer of polymorphic cells, thus giving to the cortex of this region a three-layered structure of indistinct outlines.

Fiber Tracts.—The corticifugal axons of the cells of the several layers are collected below the upper level of the large pyramidal cell layer into vertical columns which pass to the medulla as the bands of *radial fibers*. In these same columns course also the corticipetal axons. The cortex thus becomes divided vertically into cell rays and *fiber rays*, as was mentioned above. Between the fiber columns the dendronic network is known as the *interradial feltwork;* peripheral to where the fiber rays begin, this dendronic network forms the *supraradial feltwork*. At about the middle of the large pyramidal cell layer, abundant horizontal dendrons produce a distinct broad band, the *outer stripe of Baillarger*. Between the large pyramidal cell layer and the outer polymorphic cell layer, a similar

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but narrower band is known as the *inner stripe of Baillarger*. These stripes are most pronounced in the visual areas as was said above. Another band of similar nature at about the outer limit of the small pyramidal cell layer forms the *stripe of Bechterew*. Beneath the peripheral neurogliar marginal velum the dendrons of
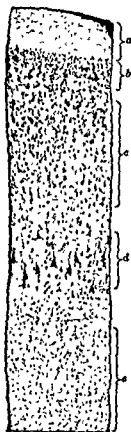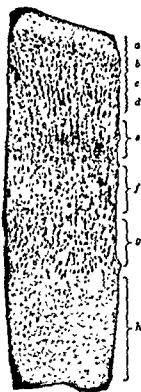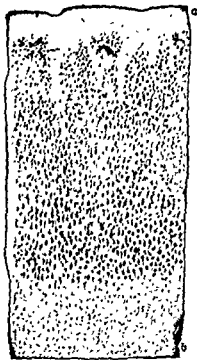
FIG. 542.   FIG. 543.   FIG. 544.

FIG. 542.—HUMAN CORTEX CEREBRI, MOTOR AREA.

a, tangential fiber layer; *b*, outer polymorphous cells; *c*, small pyramidal cells; *d*, large pyramidal cells, *e*, inner polymorphous cells. Nissl's stain. Moderately magnified. (Schlapp.)

FIG. 543.—HUMAN CORTEX CEREBRI, PARIETAL LOBE.

a, tangential fiber layer, *b*, outer polymorphous cells; *c*, small pyramidal cells; *d*, outer large pyramidal cells; *e*, granule cells; *f*, inner large pyramidal cells; *g*, inner polymorphous cells; *h*, white matter of the medulla. Nissl's stain. Moderately magnified. (Schlapp.)

FIG. 544.—HUMAN CORTEX CEREBRI, OLFACTORY REGION.

a, tangential fiber layer; *b*, white matter of the medulla. Nissl's stain. Moderately magnified. (Schlapp.)

the pyramidal cells branch and form thus a band of horizontal fibers, the *tangential fiber layer* or molecular fiber layer. These fiber bands are conspicuous only in specimens prepared with the Weigert technic. Both cortex and medulla contain abundant neuroglia cells. Those contributing almost exclusively to the marginal velum are fusiform elements with lateral tufts of short horizontal fibers, and an

expanding tuft of delicate fibers passing to the inner border of the small pyramidal cell layer. The neurogliar elements of the medulla are mostly of the long-rayed type.

THE MENINGES AND BLOOD SUPPLY

The brain and spinal cord are enveloped by the meninges, which include three fairly distinct membranes, the dura mater, arachnoid, and pia mater, and two cavities filled with lymph or a lymph-like fluid. By this arrangement the cerebrospinal axis is, as it were, suspended in fluid, and is everywhere surrounded by a watery cushion.
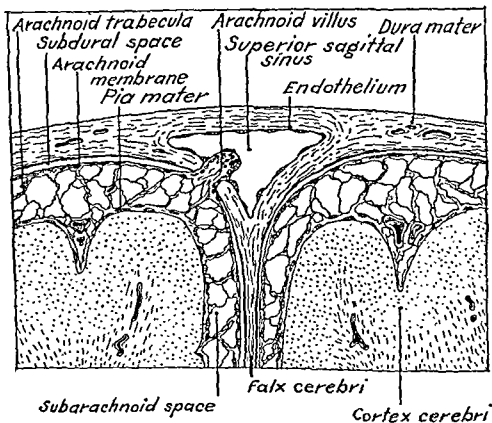
FIG. 545.—CORONAL SECTION OF MENINGES AND CEREBRAL CORTEX (SCHEMATIC) TO SHOW THE RELATION OF THE ARACHNOID VILLI TO THE DURAL VENOUS SINUS.
(Redrawn from Weed.)

Dura Mater.—The dura mater (pachymeninx) is the outermost of the three coats. Within the cranial cavity it is firmly attached to the bony walls, and serves as a periosteum for the internal surface of the bones which form the cranial cavity. Within the vertebral cavity the dura mater is distinct from the periosteum of the vertebrae, with which it is connected by loose fibrous tissue and masses of fat, which inclose large lymph spaces or chambers, lined with mesenchymal epithelium and collectively forming the *epidural space.*

The dura mater is composed of interlacing bundles of fibrous tissue containing few elastic fibers. The disposition of its fiber bundles varies somewhat in its

different portions. In its spinal portion, most of the bundles are longitudinally disposed, comparatively few passing circularly around the circumference of the vertebral canal; within the cranial vault the bundles cross at acute angles; in the falces and in the tentorium cerebelli they are radially disposed.

The cranial dura consists of two distinct layers, an outer, which is very vascular and serves as the bony periosteum, and an inner, which is but slightly vascular and may be considered as the dura proper. It is the inner layer only which is prolonged inward to form the falx cerebri and the falx and tentorium cerebelli. The venous dural sinuses of the cranium occupy clefts in the dura along the lines of attachment.
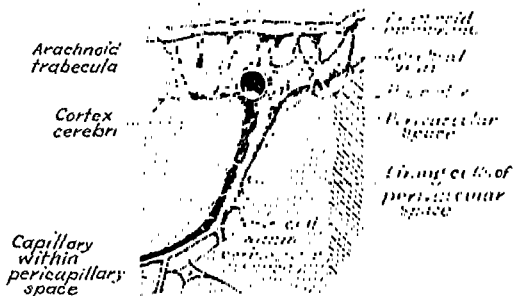
FIG. 546—SCHEMATIC DIAGRAM OF LEPTOMENINGES AND CEREBRAL CORTEX TO SHOW THE RELATION OF THE SUBARACHNOID SPACE, PERIVASCULAR CHANNELS AND NERVE CELLS.

The leptomeningeal lining cells are reflected inward for varying distances to form the lining cells of the perivascular space. (Weed.)

Although the dura mater is but poorly supplied with blood vessels, it is relatively rich in lymphatics, which open into the subdural and epidural spaces and are continuous with the perivascular and perineural lymphatics which leave the cerebrospinal cavities in company with the cerebral and spinal nerves and the larger blood vessels. In this way the lymphatics of the dura mater and its adjacent spaces are in communication with the lymphatic vessels of the eye, nose, ear and cervical lymph nodes. These communications are of special importance as indicating the path followed by certain pathological processes which involve the meninges.

Where the outer surface of the dura is not attached to the surrounding bone or connective tissue, it is covered by a thin endothelioid coat, the lining mesenchymal epithelium of the epidural spaces. Its inner surface is lined with somewhat thicker endothelioid cells, forming the wall of the subdural space. The dura

contains sympathetic fibers for its blood vessels, and also naked spinal and cerebral sensory fibers.

Arachnoid.—The arachnoid is a thin membranous sheet which is suspended between the dura and the pia mater; together with the pia mater it constitutes the *leptomeninx*. It is composed of a delicate areolar tissue which contains relatively few elastic fibers but is said to contain neither blood vessels, lymphatics nor nerves. This thin fibrous membrane is covered on either side by a layer of mesenchymal epithelium; that upon its outer surface consists of cells of considerable thickness, which are derived from the lining membrane of the inner wall
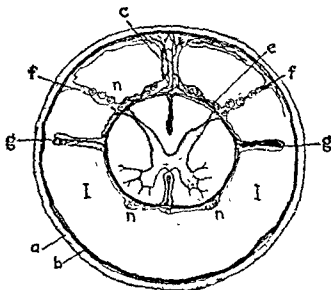
Fig. 547.—Section of the Spinal Cord and Its Membranes, from the Upper Thoracic Region.

a, dura mater; *b*, arachnoid; *c*, septum posticum; *e*, pia mater; *f*, subarachnoid trabeculae; *n*, nerve fiber bundles; *g*, ligamentum denticulatum; *I*, subarachnoid space. (From Schäfer, after Key and Retzius.)

of the subdural space; the cells upon its inner surface are thinner and are derived from the walls of the *subarachnoid space*.

Delicate septa-like bands pass from the inner surface of the arachnoid to the adjacent portions of the pia mater (Fig. 547). These processes are likewise invested by the endothelioid lining of the subarachnoid space. A similar investment clothes the processes of the *ligamentum denticulatum* of the spinal cord which attaches the pia mater spinalis on either side to the adjacent portions of the dura mater. Subarachnoid trabeculae support the nerve fibers of the dorsal roots.

A fibrous septum passing from the arachnoid to the pia mater, along a line opposite the dorsal median septum of the spinal cord, forms a fairly definite partition, the *septum posticum*. In the cervical region this is an interrupted septum, but in the thoracic and lumbar regions it becomes more or less complete.

The cranial arachnoid, in the *vicinity of the cranial sinuses*, notably the

superior longitudinal sinus, sends outward many villus-like projections or *arachnoid villi* (pacchionian bodies; *granulationes arachnoidales*). They protrude into the venous sinuses to such an extent as often to produce corresponding depressions in the inner surface of the bones of the cranial vault, into which they push, carrying before them a much attenuated portion of the dura mater. These villi are similar in structure to the membranous portion of the arachnoid. They are said to be absent at birth, small and inconspicuous in childhood, and to increase in size and number as age advances.

Fluid injected into the arachnoid or into the neighboring portions of the subarachnoid space passes readily into the lymph spaces of the dura mater, and may even be forced into the venous cavity of the cranial sinuses. While fluid thus injected may follow artificial rather than natural channels, it seems quite possible that the cerebrospinal fluid may during life find its way along such channels into the venous sinuses to the relief of excessive intracranial pressure.

Pia Mater.—The pia mater is intimately adherent to the surface of the brain and spinal cord. It follows all the irregularities of their surfaces and sends prolongations into all their sulci. In the larger fissures these invaginations form a double fold of pial tissue; in the smaller, the invaginated portions fuse to form a thin septum-like prolongation of the pia. In this particular the pia mater differs from the arachnoid, which bridges over all the sulci without dipping into any but the largest fissures. It differs also from the dura mater which, with the exception of the falces and tentorium, is not prolonged into any of the fissures or sulci of either the brain or the spinal cord.

The pia mater is a connective tissue membrane and is divisible into an inner and an outer layer. The outer layer is composed of coarse fibrous bundles the most of which in the pia mater of the spinal cord run longitudinally, while the finer fibers of the thin inner layer are circularly arranged.

Between the two layers are many blood vessels and lymphatics, the pia mater being typically a vascular membrane. The larger blood vessels are loosely embedded in the outer surface of the pia, some of them projecting into or even lying entirely within the subarachnoid space. The outer surface of the pia mater, as also the sheaths of the vessels which are loosely attached to its surface, is covered with a layer of very thin endothelioid cells derived from the lining membrane of the subarachnoid space.

The inner surface of the pia is everywhere firmly adherent to the surface of the brain and spinal cord. The slender trabeculae and septalike processes which extend into the superficial portions of these organs, consist of connective tissues whose fibrous bands are continuous with those of the membranous pia mater. In the spinal cord many of these fibrous bundles extend inward as far as the gray matter, meanwhile becoming intimately associated with neuroglia. In both the spinal cord and the brain the pial septa serve for the support of numerous blood vessels and perivascular lymphatics which are distributed through this connective tissue to all portions of the brain and spinal cord.

Within the cranium, reduplications of the pia mater, carrying between their

folds a layer of arachnoidal tissue and an extensive plexus of small blood vessels, push their way into the cerebral ventricles to form the superior and inferior *telae choroideae*. These choroid plexuses are separated from the ventricular cavities by an investment of cuboidal cells, which in fetal and infantile life are ciliated, and which are derived from and are continuous with the *ependyma cells* lining the walls of the ventricles. Thus the blood vessels of the telae choroideae, in the strictest anatomical sense, lie without and not within the cavity of the cerebral ventricles, for they are everywhere separated from those cavities by the ependyma cells, which, ontogenetically at least, form a portion of the wall of these vesicles. The cerebrospinal fluid is supposed to originate largely by process of filtration from the blood vessels of these choroid plexuses.

The pia mater contains mostly sympathetic fibers, but probably also a few sensory cerebrospinal fibers.

The peculiar arrangement of the three constituent membranes of the meninges leaves three distinct spaces or connected groups of spaces which are filled with fluid These are the epidural, subdural and subarachnoidal spaces.

Epidural Space.—The epidural space comprises a connected series of lymph cavities, which is of limited extent within the cranium, but of broad extent within the spinal canal. These spaces are lined with mesenchymal epithelium and are at many points continuous with the perivascular and perineural lymphatics and through them with the lymphatic vessels of the general systemic circulation. Obviously the epidural spaces serve as large lymphatic vessels and their cavities are consequently filled with lymph.

Subdural Space.—The subdural space has a complete lining of rather thick endothelioid cells, à mesenchymal epithelium. The walls of this cavity are formed by the dura on the outer, and the arachnoid on the inner side. The cells covering the arachnoid are of ectodermal origin according to Leary and Edwards.[4] The cavity is occupied by lymph and is continuous with the lymphatic channels of the dura, and through them with the epidural spaces and systemic lymphatics.

This space is penetrated by the outgoing cerebral and spinal nerves, which receive an investment from all three of the meningeal coats The three layers composing this investment soon lose their distinctive characteristics, fuse together, and blend with the epineurium of the nerve trunks.

Fluid injected into the subdural space may be readily forced into the lymphatics of these epi- and perineural sheaths and may thus travel to parts quite remote from the central nervous system.

Subarachnoid Space.—The subarachnoid space is lined with a thin endothelioid layer, its outer wall being formed by the arachnoid, its inner by the outer surface of the pia mater; its cavity is filled with cerebrospinal fluid, which closely resembles, yet differs somewhat in chemical composition from the lymph. It contains a few lymphocytes, estimated at five per cubic millimeter of fluid. This space is in communication through the foramen of Majendie, an opening in the roof of the fourth ventricle, with the central canal of the spinal cord and

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[4] Leary and Edwards, 1933.

the ventricular cavities of the brain. It is also thought to communicate with the cerebral ventricles at several other points.

The subarachnoid space within the cranium is of limited breadth, but within the spinal canal it is much broader and contains not only the larger blood vessels which are loosely attached to the surface of the pia, but also the many spinal nerve roots pass downward through this space toward their foramina of exit.

The spinal portion of the subarachnoid space is crossed by a posterior median septum, the septum posticum, laterally by the ligamentum denticulatum, and by several irregular but incomplete septa which, like the ligamentum posticum, connect the pia mater with the arachnoid.

The *ligamentum denticulatum* is a dense mass of fibrous tissue containing a few elastic fibers, which, beginning at the lateral surface of the pia as a complete septum, passes, by about twenty-eight serrations, across the subarachnoid space, and pushing the arachnoid before it, is attached to the inner surface of the dura mater. The serrations of the dentate ligament do not penetrate the subdural space, for around the point of their attachment the surface of the arachnoid is firmly adherent to the dura mater. Each serration is invested by an endothelioid coat continuous with the lining of the subarachnoid space.

Blood Supply.—The blood supply of the central nervous system is derived from vessels which lie within the folds of the pia mater, branches of the internal carotid and the vertebral arteries. The larger arteries form an anterior longitudinal group represented in the spinal cord by the *anterior spinal artery* and its branches, and in the brain by the vessels of the *circle of Willis* and their immediate branches.

Two sets of vessels may be said to be distributed from these sources—one of which is distributed through the pia mater to the adjacent white matter of the spinal cord and to the gray pallium of the brain; the other *penetrates the spinal cord through the anterior median fissure by a series of small fissural arteries* to be distributed to the central gray matter, and in the brain is represented by the branches of the *middle cerebral arteries* which penetrate directly to the ganglionic gray matter in the interior of the cerebrum.

In the spinal cord the vessels of the former set are mostly distributed to the white cortex. The larger branches, however, penetrate the white matter and aid in the formation of the capillary network of the gray medulla. In the brain their distribution is similar, the smaller pial vessels, the *cortical arteries*, being distributed to the cortex, which in this case is formed by the gray matter; the larger, the *medullary arteries*, penetrating the white medulla in which they break up into capillary vessels.

The veins trend in the opposite direction and in the pia mater collect into large vessels, which in the brain open into the sinuses of the dura mater, and which in the spinal cord form the ventral and dorsal median veins.

All the larger vessels receive thin fibrous investments from the pia mater; the smaller vessels and capillaries are surrounded by neuroglia (dendroglia).

There are frequent anastomoses between the larger veins. The arteries, how-

ever, are all *terminal arteries* according to Cohnheim's classification, possessing no anastomoses with the capillary areas of other vessels.

Neither brain nor cord possess true lymphatics The sole lymphatic representatives within the central nervous system are pericellular and perivascular spaces communicating with subpial spaces and ultimately through uncertain clefts and channels with the subarachnoid spaces.

The bulk of the cerebrospinal fluid is secreted by the cells of the choroid plexuses directly into the cerebral ventricles. It escapes into the subarachnoid spaces through the roof of the fourth ventricle. From here it is absorbed into the dural venous sinuses by way of the arachnoid villi. A small quantity of cerebrospinal fluid is contributed also by the blood capillaries of the central nervous system. The lymph-like fluid passes from these capillaries directly into the pericapillary spaces and thence to each nerve cell or outward through the perivascular channels to the subarachnoid spaces Besides the fluid which escapes through the venous sinuses of the dura a small amount drains also by way of the perineural spaces indirectly into the lymphatic system.[5]

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[5] Weed, 1917.

CHAPTER XVIII

THE EYE

The eye may be said to consist of the visual organ, or globe, and its appendages —the eyelids, conjunctiva and lacrimal apparatus—whose function is chiefly protective.

The globe of the eye, or eye proper, is contained within the cavity of the orbit, its posterior two-thirds being embedded in a mass of intraorbital fat whose inner surface is covered by a thin fibrous membrane or fascia which is clothed with

FIG. 548—DISSECTION OF EYELIDS AND LACRIMAL APPARATUS.

1, upper lacrimal gland; *2*, lower lacrimal gland and excretory ducts; *3*, mouths of excretory ducts; *4*, tarsal (meibomian) glands; *5*, puncta lacrimalia; *6*, lacrimal canaliculi; *7*, lacrimal sac and nasal duct; *8*, caruncula (Fox.)

mesenchymal epithelium. The epithelium is reflected from this fascia to the surface of the ocular globe, along a line just posterior to the border of the conjunctiva, whence it passes over the surface of the globe as far posteriorly as the optic nerve, on the surface of which it again becomes continuous with the mesenchymal epithelium of the fascia. Thus a serous sac or lymphatic space is formed by the parietal layer of this sac, which lines the orbital cavity, in conjunction with the visceral layer which covers the posterior two-thirds of the globe of the eye; this sac is the *capsule of Tenon*.

The anterior third of the globe is covered by a reflection, at the fornix conjunctivae, of the conjunctival layer which clothes the inner surface of the palpebrae

or eyelids. The conjunctiva is a continuation of the integument of the lid, modified so as to simulate a mucous membrane. The portion associated with the eyelid is known as the palpebral conjunctiva, that covering the eye as the ocular, bulbar or scleral conjunctiva. Where the sclera passes into the cornea, the conjunctival epithelium becomes continuous with the anterior corneal epithelium, the lamina propria blending with the corneal stroma.

FIG. 549—HORIZONTAL SECTION OF THE RIGHT EYEBALL.
(From Fox, after Magnus.)

The *globe of the eye* or *eyeball* is a spheroidal body whose surface consists of *three coats,* an outer, middle and inner, and whose contents are the vitreous and aqueous humors and the crystalline lens.

The eyeball is not a true sphere, but may be said to comprise segments of two spheres, the smaller of which is inserted into the anterior surface of the larger. The anterior or smaller segment consists chiefly of transparent tissues which permit the entrance of light. Its border nearly corresponds to the posterior margin of the ciliary body, and it may be approximately indicated by a parallel circle midway between the margin of the cornea and the equator of the eyeball. The

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anterior segment contains the cornea, the sclerocorneal junction, the anterior and posterior chambers, the aqueous humor, the iris and the ciliary body. The posterior segment comprises the posterior two-thirds of the eyeball and includes the sclera, choroid, retina, and, within these coats, the vitreous humor. The crystalline lens with its suspensory ligament forms, as it were, a partition separating the two segments.

The *optical* or *visual axis* of the eye is a horizontal, anteroposterior, imaginary line, about an inch in length, which extends from the center of the cornea through the anterior chamber, the center of the pupillary opening of the iris, the center of the crystalline lens, and the center of the vitreous humor, and reaches the fovea centralis which lies in the middle of a thickened portion of the retina, the macula lutea. The vertical and transverse axes measure about 1 millimeter less than the anteroposterior axis. Toward the inner side, at a distance of 3.5 millimeters, and about 1 millimeter below the center of the fovea centralis, is the entrance of the optic nerve. This nerve pierces the coats of the eye, its fibers spreading out in a radial manner, upon the inner surface of the retina.

The extremities of the visual axis mark the two poles of the ocular globe; the anterior extremity, lying in the center of the cornea, is in the anterior or smaller spheroidal segment, the posterior extremity, in the fovea centralis, lies in the posterior segment of the eye.

THE EXTERNAL COAT, THE FIBROUS TUNIC

The outer tunic of the eyeball (*tunica fibrosa oculi*) includes the cornea, the sclera and the sclerocorneal junction.

THE CORNEA

The cornea is a concavoconvex, transparent, colorless disk of approximately equal thickness (1 millimeter) throughout all its portions. It is nearly circular in outline, its horizontal exceeding its vertical diameter by only 0.5 millimeter; its external surface is convex, its internal surface concave. The cornea forms the anterior one-sixth of the tunica externa, and represents a spheroidal segment whose radius is somewhat shorter than that of the posterior segment of the eyeball. It is inserted into the anterior margin of the sclera much after the manner in which a watch-glass is set in its rim; hence the inner surface of the cornea possesses a slightly greater diameter than the outer.

Structure.—The cornea may be said to consist of *five layers:* the anterior epithelium; the anterior homogeneous membrane; the corneal substance; the posterior homogeneous membrane; the posterior epithelium.

Anterior Epithelium.—The anterior epithelium (*corneal epithelium, corneal conjunctiva*) at the margin of the cornea is continuous with the scleral portion of the conjunctiva. It consists of a relatively thin layer—six to eight cells deep—of stratified squamous epithelium, the deepest cells of which are elongated or columnar, the middle cells polyhedral, and the superficial cells somewhat flattened

FIG 550.—THE ANTERIOR SEGMENT OF A CHILD'S EYE; MERIDIONAL SECTION.

a, ora serrata; *b*, ciliary processes; *c*, iris; *d*, crystalline lens; *e*, ciliary muscle; *f*, ocular nnjunctiva; *g*, cornea; *h*, the capsule of the lens, partially detached. Hematein and eosin. hoto. ×10.

anterior segment contains the cornea, the sclerocorneal junction, the anterior and posterior chambers, the aqueous humor, the iris and the ciliary body. The posterior segment comprises the posterior two-thirds of the eyeball and includes the sclera, choroid, retina, and, within these coats, the vitreous humor. The crystalline lens with its suspensory ligament forms, as it were, a partition separating the two segments.

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man's membrane. At its margin the membrane is continuous with fibrous bundles which are directed outward into the ligamentum pectinatum, and, at least in some animals, through this ligament into the ciliary margin of the iris. The membrane of Descemet can be readily detached from the corneal substance by teasing. It prevents filtration of fluid from the anterior chamber into the corneal stroma.
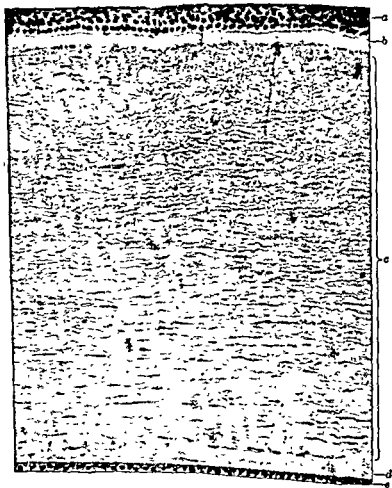
Fig 552.—From a Meridional Section of the Human Cornea.

a, anterior corneal epithelium; *b*, anterior homogeneous membrane; *c*, substantia propria; *d*, posterior homogeneous membrane; *e*, posterior corneal epithelium. Hematem and eosin. Photo. ×180.

Posterior Epithelium.—The posterior epithelial layer (*corneal endothelium*) is a mesenchymal epithelium consisting of clear, cuboidal or flattened cells, placed edge to edge, and bound together by intercellular bridges. At the margin of the cornea it is reflected over the lateral wall of the anterior chamber to the anterior surface of the iris Its cells rest upon the posterior homogeneous membrane.

All the tissues of the cornea, during life, are absolutely transparent. The elements of which they consist are of almost identical refractive indices, and about that of water, so that in fresh, or in living tissue, it is almost impossible for the

The cells at all levels are nucleated and, like the other corneal tissues, perfectly transparent. The columnar cells are often slender and much elongated, their pointed apices extending well toward the surface of the epithelial layer.

The epithelium rests directly upon the anterior homogeneous lamella.

The deeper cells of the epithelium present distinct intercellular lymphatic spaces and intercellular bridges. Between the cells are the terminal ramifications of nerve fibrils from the plexus in the corneal substance.

Anterior Homogeneous Membrane.—The anterior homogeneous membrane (*anterior basal lamella, elastic membrane of Bowman*) was formerly thought to consist of elastic tissue, but this supposition is disproved by its ready solubility on boiling, as well as by the fact that it does not react typically to the specific stains for this tissue. Bowman's membrane is apparently a homogeneous or structureless lamina except that it is slightly fibrillar at its extreme margin where it becomes continuous with the fibrous tissue of the sclera. It resembles elastic tissue in that it is highly refractive and possesses a shining glassy appearance. It does not stain readily with the ordinary dyes.

Corneal Substance.—The corneal substance (*substantia propria*) forms the greater portion of the cornea. It consists of a lamellated connective tissue, which forms about sixty fibrous layers, parallel to the corneal surface. The fibrous bundles of these lamellae, being arranged in meridional curves parallel to the surface, appear to cross one another at right angles in the central portion of the circular cornea. Other fibers, arcual fibers, pass from one layer to another; so firmly uniting them that it is impossible to tease the cornea into its component lamellae.
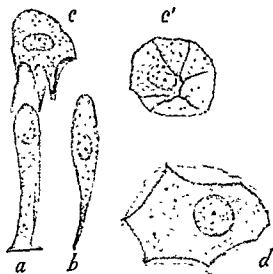
FIG. 551.—ISOLATED CELLS FROM CORNEAL EPITHELIUM OF HORSE. ×700.

a and *b*, columnar cells of the basal layer; *c*, side view of cell from middle layer; *c'*, under surface view of similar cell; *d*, surface view of cell from superficial layer. (Ellenberger and v Schumacher.)

The intervals between the fibrous layers are occupied by interlamellar cement, or ground substance, in which lymphatic channels and large flattened cells, the *corneal corpuscles*, can be demonstrated The corneal "corpuscles" are branched lamellar connective tissue cells, which occupy the large lymphatic spaces or lacunae of the interlamellar ground substance, and which send fiber-like processes into the interlacing lymphatic channels.

Posterior Homogeneous Membrane.—The posterior homogeneous membrane, or *membrane of Descemet* (*posterior basal lamella*), is similar in structure to the anterior. Like the latter, though formerly considered an elastic membrane it does not give the specific reactions of elastic tissue. It is somewhat thicker than Bow-

man's membrane, whence the terminal sensory fibrils penetrate the anterior epithelium. For a distance of several millimeters within the margin of the cornea special nerve endings (bulbous corpuscles) may also occur.

THE SCLERA

The sclera (*sclerotic coat*) is a firm opaque connective tissue membrane which forms the outermost layer of the posterior segment of the eyeball. It consists of two layers, the thick, firm, *substantia propria*, and the very thin, innermost, delicate, *lamina fusca*.

By reflected light the sclera of the adult is of a lustrous white color. In the child it has a faint bluish tint, due to the presence of pigment in the deeper layers of the child's eye which shows indistinctly through the relatively clear superficial tissues. The anterior portion of the sclera is covered by the bulbar conjunctiva and is familiarly known as the white of the eye. A yellowish patch in the vicinity of the corneal margin, known as the *pinguecula*, may be present, especially in old age. It is believed to be due to irritation from dust, leading to colloid infiltration of the conjunctival stroma.

FIG. 554—CORNEAL CELLS, ISOLATED. Highly magnified. (Waldeyer.)

That portion of the sclera which is posterior to the ocular equator is covered by the visceral layer of the capsule of Tenon except at the insertions of the straight and oblique muscles. The tendons of these muscles pierce the capsule and are obliquely inserted into the surface of the sclera in a line nearly corresponding to the equator of the eye. The tendon bundles of the muscles are directly continuous with the fibrous bundles which compose the sclera.

Substantia Propria.—The collagenous fibrous tissue of the sclera is disposed in bundles which are arranged along meridional and equatorial lines; they interlace with one another to form a dense network. A few elastic fibers are interspersed among the bundles of this network. Stellate connective tissue cells, the *scleral corpuscles*, lie in the interfascicular clefts. Occasional pigmented cells are also sometimes present.

Lamina Fusca.—The inner surface of the sclera presents a fine gauzy membrane which can be readily detached by teasing. This is the lamina fusca sclerae. It consists of delicate interlacing fibrous bundles and numerous pigmented connective tissue cells. The lamina fusca near the posterior pole is firmly adherent to the scleral substance.

At the posterior pole of the eye the sclera is pierced by the optic nerve, whose numerous bundles penetrate the coats of the eyeball and give to this portion

microscope to discover any of the structure of the cornea. After death the cornea becomes opaque and its elements are then easily distinguished.
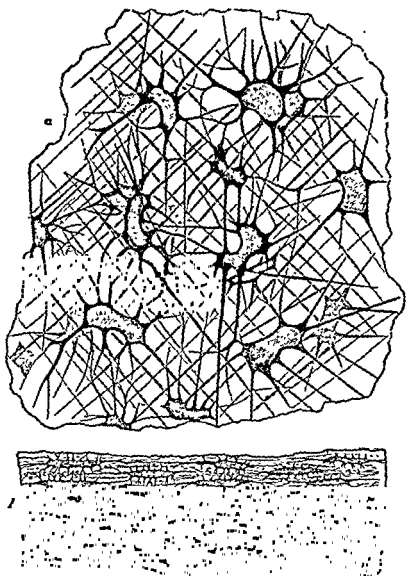
FIG. 553—CORNEAL CORPUSCLES OF THE FROG.

a, as seen in tangential section; *b*, as seen in transection of the cornea. Chloride of gold. Highly magnified. (Rollett.)

Vascular and Nerve Supply.—The cornea itself is an absolutely nonvascular tissue, having neither blood nor true lymphatic vessels. It is, however, well supplied with nerve fibers, derived from the ciliary nerves, which form an annular plexus in the sclera about the margin of the cornea, from which point bundles of naked axis-cylinders pass into the corneal substance to form a basal plexus, near the anterior homogeneous membrane. From this latter plexus, fibers are distributed to the corneal substance and to a subepithelial plexus, anterior to Bow-

to progressive increase of intra-ocular tension which causes atrophy of the optic nerve and the retina.

Blood Supply.—The sclerocorneal junction is abundantly supplied with blood from the anterior ciliary vessels, which, with the posterior conjunctival vessels, form loops at the margin of the cornea and anastomose freely with the vessels of the ciliary body. The sclera contains no true lymphatic vessels.

THE MIDDLE COAT, THE VASCULAR TUNIC

The middle tunic (*uvea, uveal tract, tunica vasculosa oculi*) includes the choroid coat, ciliary body and iris. The latter is perforated centrally by an approximately circular aperture, the pupil.

The iris divides the cavity of the anterior segment of the eye into an *anterior chamber*, included between it and the posterior or inner surface of the cornea, and a *posterior chamber*, which is bounded by the iris in front and the crystalline lens and its suspensory ligament behind. The free or pupillary margin of the iris is in light contact with the anterior surface of the lens. The posterior chamber is therefore an annular compartment.

THE CHOROID COAT

The choroid coat (*tunica choroidea*) consists of three layers: the lamina suprachoroidea, the lamina vascularis and the lamina capillaris. The function of the very vascular choroid is to supply nutrition to the outer portions of the retina.
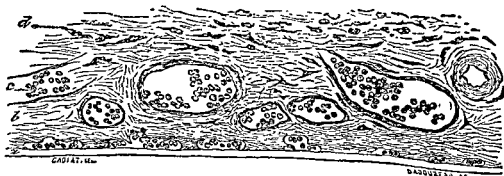
FIG 555—FROM A MERIDIONAL SECTION OF THE CHOROID COAT.

a, membrane of Bruch; *b*, the inner margin of the vascular layer. Between *a* and *b* is the capillary layer or choriocapillaris; *c*, venule containing blood corpuscles; *d*, fibrous layer of the choroid or lamina suprachoroidea. Highly magnified. (Cadiat)

Lamina Suprachoroidea.—The lamina suprachoroidea (*suprachoroid layer*) is a very delicate membrane which contains many pigmented cells and is similar in structure to the lamina fusca of the sclera.

The flattened pigmented cells are brownish-black in color from the many coarse granules which they contain, and are irregularly disposed, either separately or in groups. Lymphatic spaces occur between this layer and the sclera and communi-

of the sclera a cribrose appearance. This area of the sclerotic coat is known as the *lamina cribrosa sclerae*. It is a circular zone whose border is outlined by the entrance of the posterior ciliary arteries and the ciliary nerves. This is the thickest portion of the sclera, the coat becoming progressively thinner toward the equator of the eye; near its anterior margin it is again thickened by the tendinous insertions of the extrinsic muscles. These muscles are the superior and inferior obliques, and the four recti.

The sclera is chiefly supplied by branches from the posterior ciliary arteries, which form a wide-meshed plexus in its substance, its vessels anastomosing freely with those of the choroid coat.

The nerves of the sclera are supplied by the ophthalmic, as long and short ciliary branches. Of the extrinsic muscles attached to the sclera, the superior oblique is innervated by the fourth cerebral nerve, the trochlearis; the lateral rectus by the sixth or abducens; and the remaining four by the oculomotor or third cerebral (cranial) nerve.

THE SCLEROCORNEAL JUNCTION

The sclerocorneal junction (Fig. 556) is a narrow circular zone at the margin of the cornea, where it is inserted into the sclera. Across this narrow zone the fibrous bundles of the opaque sclera are continued directly into the similar, though perfectly transparent, bundles of the corneal substance.

The anterior or outer surface of this zone is covered by the ocular portion of the conjunctiva. Its epithelium is of the stratified squamous variety and is continuous with the anterior epithelium of the cornea.

From the inner surface of this junctional zone the anterior extremities of the muscle fibers composing the ciliary muscle take their origin. The fibers of this muscle intermingle with the marginal fibers of the posterior homogeneous layer of the cornea to form the *ligamentum pectinatum*, which connects the sclerocorneal junction with the base of the iris. This pectinate ligament is very much more highly developed in certain animals, *e.g.*, cow and horse, than in man.

Toward the inner side of the scleral margin and near the border of the cornea is the *canal of Schlemm* (*sinus venosus sclerae*). This is an annular venous channel (or network of channels), draining into the anterior ciliary veins. Though venous in character it serves also as a drainage channel for the lymphatic *spaces of Fontana*, which lie in the lateral wall of the anterior chamber and between the fiber bundles of the ligamentum pectinatum.[1] The spaces of Fontana are true lymphatic spaces and are in communication with the anterior chamber of the eye.

Through the canal of Schlemm, the aqueous humor of the anterior chamber is put into communication with the veins of the sclera, and a system is thus formed by which the intra-ocular pressure is maintained at normal. A blocking of the canal of Schlemm interferes with the drainage of the anterior chamber, and produces the serious pathologic condition of the eyeball, known as *glaucoma*, due

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[1] Uribe, 1921.
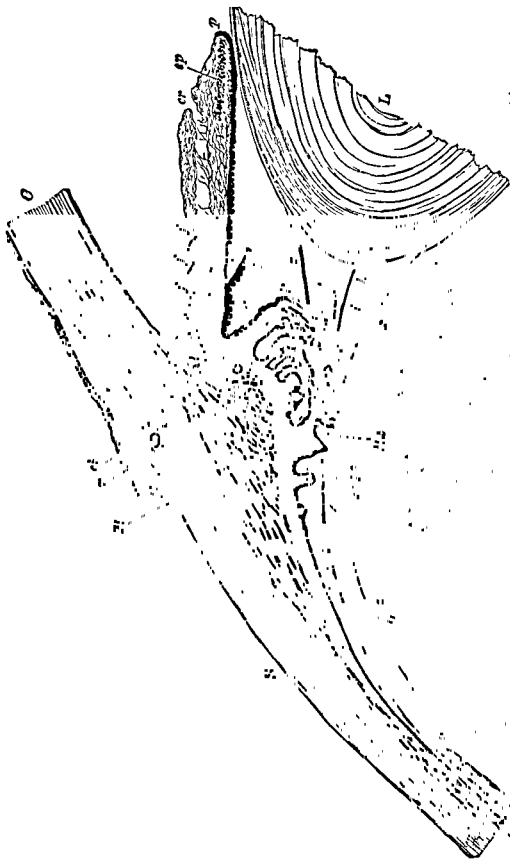
portion or orbiculus of the ciliary body; *Pe*, retinal pigment epithelium; *, *, outer or pigmented margin of the iris; *Pc*, retinal pigment epithelium; *Ic*, inner, nonpigmented layer of the ciliary epithelium; *S*, sclera; *s*, canal of Schlemm; *Pe*, inner, nonpigmented layer of the ciliary muscle; *R*, retina, *r*, radial fibers of the ciliary muscle; layer of the ciliary epithelium; *v*, outer pigmented layer of the retinal epithelium; *z*, *z*, *z*, *st*, circular muscle of the iris, the sphincter pupillae; *v*, outer pigmented layer of the retinal epithelium; *z*, *z*, *z*, suspensory ligament of the lens. ×16 (After Fuchs.)

cate through the interfascicular lymphatic clefts of the sclera with the capsule of Tenon.

The fibers of this layer are not only distributed in its own plane but pass *obliquely to the lamina fusca, thus loosely attaching the suprachoroid layer to the* sclera. Similar, obliquely disposed fibers pass to the deeper portions of the choroid, with the fibers of which they blend.

Lamina Vasculosa.—The lamina vasculosa (*vascular layer, choroid proper*), *so called because it contains the ramifications of the ciliary arteries and veins,* is by far the thickest of the three layers of the choroid. It may be arbitrarily separated into an outer stratum, consisting chiefly of dense interlacing bundles of connective tissue fibers which inclose only the larger blood vessels, and an inner stratum of similar structure, but *everywhere permeated by a close network of small vascular twigs.* So dense is this network near the posterior pole of the eye, as to give the layer the appearance of an almost continuous sheath of small blood vessels.

Lamina Capillaris.—Within the vascular layer is the capillary membrane (*lamina capillaris, lamina choriocapillaris, tunica Ruyschiana*), which contains an exceedingly close-meshed capillary network. This network is specially dense near the macula lutea at the posterior pole of the eyeball. Its inner surface forms a very thin homogeneous membrane, the *lamina basalis, lamina vitrea* or *membrane of Bruch,* which increases somewhat in thickness as age advances. The inner surface of the lamina basalis is indented by the bases of the adjacent pigment cells of the retina Anteriorly the vessels of the choriocapillaris, like those of the vascular layer, become continuous with the vessels of the ciliary body and iris.

Between the pars vascularis and the choriocapillaris may be distinguished a narrow dense fibro-elastic boundary zone, free of pigment. In ruminants this layer becomes pronounced, due to the presence of robust connective tissue fibers, and is known as the *tapetum fibrosum.* This layer gives to the eyes of ruminants their characteristic metallic luster. In the eyes of carnivora and certain fishes the tapetum is composed of rectangular epithelioid cells, filled with peculiar glistening crystals giving to these eyes an iridescent sheen, and is known as the *tapetum cellulosum.*

THE CILIARY BODY

The ciliary body (*corpus ciliare*) represents the thickened anterior border of the choroid coat. It is, therefore, of annular shape and occupies a zone whose posterior border blends with the choroid at a point opposite the ora serrata of the retina, and whose anterior margin is continued into the iris opposite the sclero-corneal junction.

The ciliary body may be said to consist of three structures arranged in layers of varying thickness: the *ciliary muscle,* the *fibrous layer* with its *ciliary processes* and that portion of the pigmented epithelium of the retina which constitutes the *pars ciliaris retinae* or *ciliary epithelium,* and covers the inner surface of the

Appended to the inner surface of the fibrous layer are from 60 to 80 meridionally disposed folds of connective tissue which radiate from the base or outer margin of the iris to the margin of the choroid opposite the ora serrata. These are the *ciliary processes*. The longer measure about 2.5 millimeters; the shorter, comprising about one-third of the entire number, measure only about 0 2 millimeter. Their inner or free surface is covered by the pigmented retinal epithelium, and within these processes are contained the greater portion of the pigmented connective tissue cells of the ciliary body. Each fold is much deeper (about 1 millimeter) toward its axial margin and becomes progressively diminished in height toward the choroid.

The pigmented epithelial layer is here and there invaginated into the fibrous tissue of the ciliary processes to form ampullate recesses (the *ciliary glands*), which somewhat resemble true secreting glands. These so-called glands have been supposed to be concerned in the secretion of the aqueous humor. They are probably not true secreting glands, but represent mere invaginations of the epithelium.

Ciliary Epithelium.—The ciliary epithelium (*pars ciliaris retinae*) consists of a double layer of epithelial cells, continuous posteriorly with the retina, and in front with the pars iridica retinae. The superficial (innermost) cells present a clear or slightly granular cytoplasm with a centrally situated nucleus. Their cytoplasm is but slightly pigmented, and ofttimes is indistinctly rodded or fibrillated. In shape, these cells are of the low columnar type, but they become progressively flattened toward the iris, where they are continuous with the pars iridica retinae. They represent a continuation of the sustentacular cells of the retina.

The cells of the deeper (outer or anterior) layer vary in height from a low columnar at the ora serrata to a somewhat flattened cell near the iridal margin, and are continuous with the pigmented cell layer of the retina This cell layer is deeply pigmented, the entire cytoplasm being filled with the dark brown pigment granules. The nucleus, however, as in the pigmented cells of the choroid, contains no pigment, and therefore, in unstained preparations, appears under the microscope as a clear opening in the dark background of pigmented cytoplasm.

THE IRIS

The iris (Figs. 550, 556) forms an annular curtain which projects from the anterior margin of the ciliary body toward the axis of the eye It presents a central circular opening, the pupil, which lies in the visual axis.

The iris is suspended in the aqueous humor, its pupillary margin resting gently upon the anterior surface of the lens, its base or ciliary margin being separated from the lens by an interval, the posterior chamber, which is also filled by the aqueous humor.

The iris may be said to consist of *three layers*: the external epithelium, the fibrous stroma and the internal epithelium.

External Epithelium.—The external epithelium (*endothelium of the iris*) is a mesenchymal epithelium continuous at the margin of the anterior chamber with the posterior epithelial layer of the cornea, which appears to be reflected upon the

ciliary body. The suspensory ligament of the crystalline lens is attached to the inner surface of the retinal epithelium of the ciliary processes and grooves.

Ciliary Muscle.—The ciliary muscle consists of an annular mass of nonstriated fibers which arise from the inner surface of the sclera near the sclerocorneal junction, and are inserted into the entire breadth of the fibrous mass of the ciliary body as far back as the anterior margin of the choroid. The muscle fibers are divisible into three sets, according to the direction of their long axis; these are the *meridional*, the *radial* and the *circular*.

Meridional Fibers.—The meridional fibers form the outer and greater portion of the muscle. They begin just posterior to the corneal margin, taking their origin from the inner surface of the sclera, and radiate backward in a meridional direction for a variable distance, to be finally inserted into the fibrous bundles of the posterior half of the ciliary body (ciliary ring), the longest fiber bands passing as far back as the choriociliary junction, where they are attached to the anterior margin of the choroid.

Radial Fibers.—The radial fibers simulate the meridional fibers in that they radiate from the corneal margin. They pursue, however, a shorter course. From their origin they pass backward with a sharp inward curve to assume a direction which approaches that of the radii of the ocular globe (hence their name); they are inserted into the anterior half of the fibrous layer of the ciliary body. Their radial disposition becomes progressively more apparent toward the axial margin of the ciliary body. These fibers are far less numerous than the meridional.

Circular Fibers.—The circular fibers comprise numerous small nonstriated muscle bundles which are interspersed among the bundles of radial fibers. They are disposed in a circular direction about the axial margin of the ciliary body on its outer surface, and hence are in relation with the inner surface of the sclerocorneal junction and the outer margin of the base of the iris. The circular muscle fibers are also interspersed among the fibers of the ligamentum pectinatum, which pass in a radial manner from the margin of the posterior homogeneous membrane of the cornea to the base of the iris and anterior margin of the ciliary body. The circular fibers are said to be deficient or even absent in myopic eyes, but are exaggerated in hypermetropic eyes.

The dispositon of the ciliary muscle fibers is such that during contraction the fibrous ciliary body and the base of the iris are drawn forward, the choroid is made tense, and the suspensory ligament of the lens is relaxed. The lens then becomes more nearly spherical because of its own plasticity.

Fibrous Layer.—The fibrous layer of the ciliary body consists of connective tissue, and connects the fibrous portion of the choroid to the similar tissue of the iris. It is formed by a reticulum of the fine fibers in the meshes of which are numerous lamellar and a few pigmented cells. Buried within the outer portion of this fibrous mass and intermingling with its fibers are the fiber bundles of the ciliary muscle. Into the inner portion of the fibrous layer a vascular plexus is continued from the vascular and capillary layers of the choroid; branches of the ciliary arteries communicate with this plexus.

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Embedded in the fibrous stroma, near its pupillary margin, is a small bundle of nonstriated muscle fibers, which are circularly disposed, to form the so-called *sphincter muscle* of the iris. Its fibers are distributed in a plane parallel to the surface of the iris, and within the inner (posterior) part of its fibrous stroma. They are most abundant near the pupillary margin, and become progressively thinner toward the base of the iris. Internally to the sphincter muscle, and in contact with the basement membrane of the internal epithelium, is an incomplete layer, more distinct toward the ciliary margin of the iris, which contains radially disposed smooth muscle fibers, the *dilator muscle* of the iris, apparently of ectodermal origin. Mydriatics (*e.g.*, atropine) produce an enlargement of the pupil, presumably through inhibition of the constrictor and stimulation of the dilator muscles; miotics (*e.g.*, morphine, eserine, pilocarpine) however, produce a contrary effect.

The stroma of the iris is exceedingly vascular, the arteries and veins being meridionally disposed, the capillaries forming an irregular plexus. Near the pupillary margin the vessels form a rich capillary anastomosis, the *circulus minor*. The entering arteries likewise form a *circulus major* by anastomoses at the ciliary margin of the iris.

Internal Epithelium.—The internal epithelium (*posterior epithelium, pars iridica retinae*) resembles that of the ciliary body or pars ciliaris retinae, with which it is continuous. The innermost (superficial) layer of epithelial cells, in the iridal epithelium, is deeply pigmented and somewhat flatter than in the ciliary body. The pigmentation is so deep that in the adult iris it is scarcely possible to distinguish the two epithelial layers. These can, however, be readily seen in the fetal eye, and even in that of the child.

THE ANTERIOR CHAMBER

The *anterior chamber* is bounded in front by the posterior (internal) surface of the cornea, and behind by the anterior surface of the crystalline lens and the anterior (external) aspect of the iris. It contains the aqueous humor presumably largely a filtration product from the numerous blood vessels of this region, in part a secretion product of the ciliary epithelium. Its anterior boundary is convex, its posterior concave, and its circular margin is limited by an area which is known as the *iridocorneal angle*.

At this angle the mesenchymal epithelium is reflected from the posterior surface of the cornea upon the anterior surface of the iris. The latter portion of the epithelial layer is incomplete, since it presents numerous openings which communicate with the lymphatic spaces between the fibers of the ligamentum pectinatum and ciliary muscle. These lymphatic recesses, the *spaces of Fontana* or *pectinate villi*, drain into the canal of Schlemm.

The *ligamentum pectinatum* consists of fibers which arise from the margin of Descemet's membrane, and pass backward and inward, in a radial direction, to the fibrous stroma of the iris and ciliary body. Viewed from the cavity of the

anterior surface of the iris. At the pupillary border it is also continuous with the *internal epithelium of the iris* (pars iridica retinae). The cells of the anterior or external epithelium are very much flattened and almost endothelial in appearance; at occasional intervals the epithelium is incomplete. These intervals occur either near the pupillary or the ciliary margin, and correspond to recesses which open directly into the fibrous stroma of the iris and become continuous with its lymphatic interstices.

To the naked eye the anterior surface of the iris presents an uneven appearance, which is apparently due to the presence of slight meridional ridges, with shallow intervals, which extend from the pupillary margin of the iris to its outer border. The lighter radial and circular markings are due to the blood vessels.

Fibrous Stroma.—The fibrous stroma of the iris (*pars choroidalis iridis, pars uvealis iridis*) consists of a loose, spongy connective tissue of an almost embryonal type. Its fibers are scanty and are gathered into small bundles, which interlace somewhat, but which are for the most part disposed in a meridional direction. This disposition is especially noticeable near the ciliary margin.
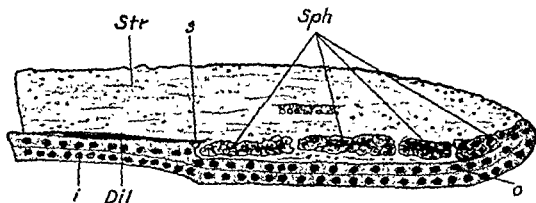
FIG. 557.—MERIDIONAL SECTION OF PUPILLARY BORDER OF HUMAN IRIS.

i, inner epithelial layer of pars iridica retinae; *o*, outer epithelial layer; *Sph*, sphincter muscle; *Dil*, dilator muscle, *s*, epithelial 'spur'; *Str*, iridical stroma. Newborn infant. (Szily)

The fibrous stroma is very rich in connective tissue cells, which are mostly stellate and branch and interlace freely. They contain more or less brownish pigment, which is most abundant near the posterior (inner) surface. The color of the iris, when viewed with the naked eye, is dependent upon the depth of pigmentation in these connective tissue cells, as well as in the cells of the internal epithelial layer, and to the relative transparency of the stroma. In dark blue and black eyes the stroma pigment is scanty, and the very dark epithelial pigment shows through the more anterior clear layers of the iris. In the brown eye the stroma pigment is dense and opaque. A gray color is produced by a scanty stroma pigment clouded by a rather dense fibrous stroma. In the eyes of albinos the iris lacks pigment altogether; the pink color of the iris is due to the blood in the numerous vessels of the stroma.

The retina presents on its inner surface a slightly elevated yellow spot, the *macula lutea*, which lies exactly at the posterior pole of the visual axis. The *fovea centralis* is the slight depression in the center of the macula lutea, and is the result of an apparent thinning of the retinal layers at this point.

The *papilla optica*, or entrance of the optic nerve (*optic disk, colliculus nervi optici*), also forming a slight elevation with a central depression, *the physiologic excavation* (*porus opticus*), is placed 3.5 to 4 millimeters to the nasal side of the macula lutea, and at a slightly lower horizontal plane.

FIG 558—THE DEVELOPING EYE IN MERIDIONAL SECTION.

A, early; *B*, later stage *E, E*, ectoderm; *L*, lens; *M, M*, mesoblast; *a*, optic vesicle, protruding from, *b*, the first cerebral vesicle, *c*, a thickening of the ectoderm, primordium of the lens; *p*, outer coat of the optic vesicle, primordium of the retinal epithelium; *r*, inner wall of the vesicle, primordium of the neural portion of the retina. (Fuchs)

Development of the Eye

A brief statement on the development of the organ will make clearer the description of the several layers of the retina. The retina is developed as an evagination of the first cerebral vesicle, and is, therefore, to be regarded as a detached lobe of the cerebrum itself. The evagination or *optic vesicle* grows forward in the embryo, and soon forms a flask-shaped process whose expanded extremity is early infolded in a cup-like manner forming the *optic cup*. The peripheral layer of the cup becomes the pigmented layer, the lining layer differentiates into the neural layers, of the retina. The inferior surface of this optic cup and the connecting *optic stalk* at first present a slit-like deficiency, the *choroidal fissure*, into which grows the mesodermal tissue which ultimately forms the vitreous humor and conveys the central artery of the optic nerve. The indented extremity of the optic cup is soon occupied by the developing lens, which arises, under the influence of the optic cup itself, but is formed from the overlying area of the epidermal ectoderm.[2]

FIG. 559—SCHEMATIC RECONSTRUCTION OF THE DEVELOPING EYE.

a, optic cup; *s*, choroidal fissure; *s₁*, optic nerve; *L*, developing lens. (Fuchs)

According to certain investigators[3] the definitive vitreous humor is preceded by a primitive structure in the form of a loose-meshed reticulum of protoplasmic fibers (cytodesmata) derived from, and in continuity with, both the lens and the retina, hence ectodermal in origin. This primitive vitreous body is subsequently invaded by vascular

[2] Lewis, W H , 1904
[3] Szily, et al , 1908

anterior chamber the fibers of this ligament, with the intervening spaces of Fontana, present a toothed appearance; the ligament derives its name from this peculiarity.

THE POSTERIOR CHAMBER

The posterior chamber is an annular cavity, somewhat triangular or trapezoidal in transection, whose lumen, like that of the anterior chamber, is occupied by aqueous humor, suspended in which are the fibers of the suspensory ligament of the crystalline lens.

It is limited anteriorly by the internal surface of the iris, and antero-externally by the ciliary processes. Its postero-internal boundary is formed by the marginal portion of the lens, together with the adjacent portion of the hyaloid membrane, which incloses the vitreous humor.

THE INTERNAL COAT, THE NERVOUS TUNIC

The internal coat of the eyeball (*tunica nervosa oculi*) is divisible into three portions: the pars optica retinae or *retina* proper, the pars ciliaris retinae and the pars iridica retinae.

The last two portions, though morphologically continuous with the pars optica retinae, differ therefrom in their physiological function; they respectively form the innermost layer of the ciliary body and iris. As such they have already been described.

THE RETINA

The retina (*pars optica retinae, neurolemma*) may be said to be formed by the radial expansion of the fibers of the optic nerve which enter the eye at the inner side of its posterior pole, piercing the sclera and choroid and spreading out over the inner surface of the eyeball.

These nerve fibers arise from groups of nerve cells which are disposed in layers to form the optic and retinal ganglia (*ganglion nervi optici* and *ganglion retinae*). The association of nerve cells and fibers with their supporting tissues forms the inner, *cerebral*, or *neural portion* of the retina. The dendritic arborizations of many of these nerve cells lie within the outer half, or *neuro-epithelial portion* of the retina.

The retina may be said to extend forward from the entrance of the optic nerve (optic disk) as far as the posterior margin of the ciliary body, where it apparently ends abruptly with an indented border, the *ora serrata*. From this border the retina is continued farther forward, but only as the dark pigmented layers of the ciliary processes and iris. In the usual preparations these layers contrast intensely with the opaque white color of the true retina. Like all the other tissues which are placed in the optical axis of the eye, the retina, during life, with the exception of its pigment layer, is perfectly transparent, but becomes opaque immediately after death or local injury.

The retina presents on its inner surface a slightly elevated yellow spot, the *macula lutea*, which lies exactly at the posterior pole of the visual axis. The *fovea centralis* is the slight depression in the center of the macula lutea, and is the result of an apparent thinning of the retinal layers at this point.

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outer or basal portion of the cell being relatively free from pigment. In an eye which is shaded from the light, or in one removed in comparative darkness, the pigment has apparently retracted until it lies entirely with the body of the cell. Even under these conditions the extreme base of the cell frequently presents a narrow zone which is relatively free from pigment. Similar changes in the disposition of the pigment undoubtedly occur in the living eye under the influence of exposure to varying degrees of light

The function of this pigment and of the peculiar changes in its disposition is still somewhat speculative, but it may, without doubt, be safely asserted that these phenomena are concerned with the renewal of the *visual purple* of the outer segments of the rods after the same has been bleached by exposure to light. Possibly these changes possess a stimulant action upon the neuro-epithelial elements. Herrick [5] suggests that both the fuscin of the cells of the pigment epithelium and

Fig. 561.— Pigmented Epithelium of the Retina, Viewed in Transection.

×500. (Fuchs.)

the rhodopsin of the bacillary epithelium are concerned with the adaptation of the eye to different intensities of light, rather than with the specific receptor function itself.

Rod and Cone Layer.—The rod and cone layer (*bacillary layer*) consists of a series of columnar elements which are disposed in a palisade-like manner, and whose narrow extremities are embedded in the surface of the layer of pigment epithelium. The rod and cone layer contains elements of two distinct types, the rods and the cones, specialized receptors of the *rod* and *cone visual cells*, and very similar to each other in their structure Each rod and each cone visual cell consists of two distinct portions, the outer of which, alone, lies in the bacillary layer; the inner portion is included in the outer nuclear layer of the retina. The outer portion is cytoplasmic, and its broad base rests upon the external limiting membrane; the inner portion is narrow, nucleated near its center, and extends entirely through the outer nuclear layer.

The Rods.—The outer, cytoplasmic, or bacillary portion of each rod visual cell consists of a somewhat thickened spheroidal base, the inner segment, and an outer filamentous extremity, the outer segment. These two segments are quite as distinct in fresh unstained tissue as in fixed and stained preparations, the distinction being due to the fact that the inner segment of each rod, while finely granular and easily stained, is also singly refractive; the outer homogeneous segment, on the other hand, not only stains with difficulty but is doubly refractive or anisotropic. The outer, therefore, under all conditions appears bright and lustrous as compared with the isotropic inner segment. The outer segment is said to be covered by a delicate sheath of neurokeratin, and to consist of a substance chemically very similar to that of the myelin of medullated nerve fibers.

The outer segment contains the *visual purple* or *rhodopsin* which, during life, is rapidly bleached by exposure to light, and is as rapidly renewed through the agency of the pigment epithelium.

[5] Herrick, 1916

mesenchyma, the two tissues uniting to produce the definitive vitreous. The hyaloid membrane, surrounding the vitreous body, and the fibers of the suspensory ligament of the lens are thought by some to represent the persistent peripheral remains of the original ectodermal stroma. Others, among them most recently Baldwin,[4] describe the origin of the suspensory ligament from mesenchyma.

Failure of closure on the part of the choroidal fissure gives rise to various degrees of a defect known as *coloboma*. This condition may appear simply as a shallow cleft in the iris, or as a more or less extensive fissure in the retina or even the optic nerve, which seriously interferes with vision.

FIG. 560—VERTICAL SECTION OF BACIL-LARY LAYER OF RETINA OF A TWENTY-FOUR-YEAR-OLD MAN, IN THE REGION OF THE FOVEA CENTRALIS.

1, pigment layer; *2*, rods and cones, the outer segment stained dark; *3*, fiber baskets ("rod sockets"), comprising the terminal fibrils of Müller's fibers; *4*, external limiting membrane; *5*, nucleus of cone; *6*, nucleus of rod visual cell. (Eisler.)

Layers of the Retina

The retina may be said to consist of ten layers, which from without inward are: (1) the pigment epithelium, (2) the layer of rods and cones, (3) the external limiting membrane, (4) the outer nuclear layer, (5) the fiber layer of Henle, (6) the outer reticular layer, (7) the inner nuclear layer, (8) the inner reticular layer, (9) the ganglion cell layer and (10) the nerve fiber layer.

To these several layers an additional one, the internal limiting membrane, is frequently added. The first five of these layers are contained within the *neuro-epithelial portion* of the retina, the last five form its *cerebral* or *neural* portion.

Pigment Epithelium.—The pigment epithelium (*layer of pigmented cells*) consists of a single layer of columnar epithelial cells whose bases, of generally hexagonal outline, rest upon and are firmly adherent to the inner surface of the choroid coat, and from whose free borders irregular processes extend inward between the elements of the rod and cone layer. These epithelial cells have a finely granular cytoplasm. Their nucleus is oval, somewhat flattened, and placed near the base of the cell; it is, however, obscured or even entirely hidden by the mass of dark pigment granules (fuscin) by which the cytoplasm of the cell is more or less completely filled.

The disposition of the pigment within the epithelial cell apparently corresponds to, and is dependent upon, the effect of light upon the retina. In an eye exposed to the action of light *at the instant of death*, the pigment granules accumulate in the irregular processes of the cells which surround the rods and cones, the

⁴ Baldwin, 1912

outer or basal portion of the cell being relatively free from pigment. In an eye which is shaded from the light, or in one removed in comparative darkness, the pigment has apparently retracted until it lies entirely with the body of the cell. Even under these conditions the extreme base of the cell frequently presents a narrow zone which is relatively free from pigment. Similar changes in the disposition of the pigment undoubtedly occur in the living eye under the influence of exposure to varying degrees of light.

The function of this pigment and of the peculiar changes in its disposition is still somewhat speculative, but it may, without doubt, be safely asserted that these phenomena are concerned with the renewal of the *visual purple* of the outer segments of the rods after the same has been bleached by exposure to light. Possibly these changes possess a stimulant action upon the neuro-epithelial elements. Herrick [5] suggests that both the fuscin of the cells of the pigment epithelium and

FIG. 561.— PIGMENTED EPITHELIUM OF THE RETINA, VIEWED IN TRANSECTION.

×500. (Fuchs.)

the rhodopsin of the bacillary epithelium are concerned with the adaptation of the eye to different intensities of light, rather than with the specific receptor function itself.

Rod and Cone Layer.—The rod and cone layer (*bacillary layer*) consists of a series of columnar elements which are disposed in a palisade-like manner, and whose narrow extremities are embedded in the surface of the layer of pigment epithelium. The rod and cone layer contains elements of two distinct types, the rods and the cones, specialized receptors of the *rod* and *cone visual cells*, and very similar to each other in their structure. Each rod and each cone visual cell consists of two distinct portions, the outer of which, alone, lies in the bacillary layer; the inner portion is included in the outer nuclear layer of the retina. The outer portion is cytoplasmic, and its broad base rests upon the external limiting membrane; the inner portion is narrow, nucleated near its center, and extends entirely through the outer nuclear layer.

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The outer segment contains the *visual purple* or *rhodopsin* which, during life, is rapidly bleached by exposure to light, and is as rapidly renewed through the agency of the pigment epithelium.

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mesenchyma, the two tissues uniting to produce the definitive vitreous. The hyaloid membrane, surrounding the vitreous body, and the fibers of the suspensory ligament of the lens are thought by some to represent the persistent peripheral remains of the original ectodermal stroma. Others, among them most recently Baldwin,[4] describe the origin of the suspensory ligament from mesenchyma.

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To these several layers an additional one, the internal limiting membrane, is frequently added. The first five of these layers are contained within the *neuro-epithelial portion* of the retina, the last five form its *cerebral* or *neural* portion.

Fig. 560.—Vertical Section of Bacillary Layer of Retina of a Twenty-four-year-old Man, in the Region of the Fovea Centralis.

*. . . pigment layer; 2, rods and cones; the . . . limiting membrane, 5, nucleus of cone; 6, nucleus of rod visual cell. (Eisler.)

Pigment Epithelium.—The pigment epithelium (*layer of pigmented cells*) consists of a single layer of columnar epithelial cells whose bases, of generally hexagonal outline, rest upon and are firmly adherent to the inner surface of the choroid coat, and from whose free borders irregular processes extend inward between the elements of the rod and cone layer. These epithelial cells have a finely granular cytoplasm. Their nucleus is oval, somewhat flattened, and placed near the base of the cell; it is, however, obscured or even entirely hidden by the mass of dark pigment granules (fuscin) by which the cytoplasm of the cell is more or less completely filled.

The disposition of the pigment within the epithelial cell apparently corresponds to, and is dependent upon, the effect of light upon the retina. In an eye exposed to the action of light at the instant of death, the pigment granules accumulate in the irregular processes of the cells which surround the rods and cones, the

4 Baldwin, 1912.

outer or basal portion of the cell being relatively free from pigment. In an eye which is shaded from the light, or in one removed in comparative darkness, the pigment has apparently retracted until it lies entirely with the body of the cell. Even under these conditions the extreme base of the cell frequently presents a narrow zone which is relatively free from pigment. Similar changes in the disposition of the pigment undoubtedly occur in the living eye under the influence of exposure to varying degrees of light.

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Fig. 561.— Pigmented Epithelium of the Retina, Viewed in Transection.

×500. (Fuchs)

the rhodopsin of the bacillary epithelium are concerned with the adaptation of the eye to different intensities of light, rather than with the specific receptor function itself.

Rod and Cone Layer.—The rod and cone layer (*bacillary layer*) consists of a series of columnar elements which are disposed in a palisade-like manner, and whose narrow extremities are embedded in the surface of the layer of pigment epithelium. The rod and cone layer contains elements of two distinct types, the rods and the cones, specialized receptors of the *rod* and *cone visual cells*, and very similar to each other in their structure. Each rod and each cone visual cell consists of two distinct portions, the outer of which, alone, lies in the bacillary layer; the inner portion is included in the outer nuclear layer of the retina. The outer portion is cytoplasmic, and its broad base rests upon the external limiting membrane; the inner portion is narrow, nucleated near its center, and extends entirely through the outer nuclear layer.

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The outer segment contains the *visual purple* or *rhodopsin* which, during life, is rapidly bleached by exposure to light, and is as rapidly renewed through the agency of the pigment epithelium.

⁵ Herrick, 1916.

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1, pigment layer; *2*, rods and cones, the outer segment stained dark; *3*, fiber baskets ("rod sockets"), comprising the terminal fibrils of Muller's fibers; *4*, external limiting membrane; *5*, nucleus of cone; *6*, nucleus of rod visual cell (Eisler.)

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The disposition of the pigment within the epithelial cell apparently corresponds to, and is dependent upon, the effect of light upon the retina. In an eye exposed to the action of light at the instant of death, the pigment granules accumulate in the irregular processes of the cells which surround the rods and cones, the

[4] Baldwin, 1912.

The Cones.—The cones resemble the rods in structure, but their cytoplasmic portion is shorter, the inner segment of which is several times as broad (35 μ by 7 μ). The outer anisotropic segment is especially short and does not contain visual purple, which the isotropic basal segment, whose fibrillated ellipsoid occupies a somewhat greater proportion of its length than is the case with the homologous rod segment, rests directly upon, and may even project through the external limiting membrane. The inner or nucleated portion, therefore, begins as a broad nucleated mass, equal in diameter and continuous with the bacillary portion of the cone element, to which it is ofttimes united by a slightly constricted neck. In this inner portion, just within the external limiting membrane, is the cone nucleus; it differs from the rod nucleus in that it stains less deeply, presents no transverse striations, and frequently incloses a distinct nucleolus. From its nucleated portion the *cone fiber* is continued as a rather broad cytoplasmic filament straight inward to the border of the nuclear layer, where it terminates in an expanded portion or *cone foot*, from the flattened inner surface of which the fine filaments penetrate the margin of the outer reticular layer.

The outer segments of both rods and cones are embedded in the cells of the pigment layer, whose delicate filamentous processes project between the rods and cones, frequently extending almost to the external limiting membrane. Both rods and cones are hexagonal or nearly circular in transection. The slight intervals between the neighboring elements and the processes of the pigment epithelium are occupied by

FIG 563.—DIAGRAM OF THE ROD AND CONE VISUAL CELLS, AND THEIR RESPECTIVE BIPOLAR NEURONS. (Schwalbe)

m.l.e., external limiting membrane; n.l.e., external nuclear layer; r.l.e, external reticular (molecular) layer; n.l.i., internal nuclear layer (layer of rod and cone bipolars).

a homogeneous fluid, probably a somewhat modified lymph. The rods far outnumber the cones; three to four rods generally appear between two successive cones. The total number of cones in the human retina has been estimated at 7,000,000; that of rods at 130,000,000.

External Limiting Membrane.—The external limiting membrane (*membrana limitans externa*) consists of the flattened and amalgamated extremities of the sustentacular cells (Müller's fibers), which form the chief supporting tissue, the neuroglia elements, of the retina, and which extend from the extreme inner surface outward to the external limiting membrane. It will therefore be more con-

Both segments, but especially the inner, under favorable conditions, present faint longitudinal striations. These striations, when present, are most distinct in the outer half of the inner rod segment where they form the so-called *ellipsoid;* they are generally interpreted as due to linear surface grooves in the outer segments, and to fibrils in the ellipsoid. The outer filamentous segment of each rod sometimes exhibits transverse markings, possibly indicating a minute structure which is comparable to a series of superposed disks.
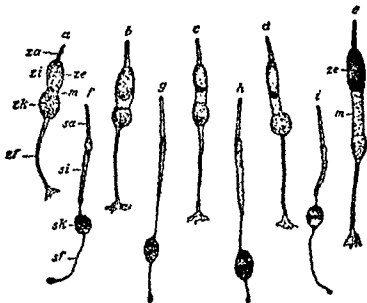
FIG. 562.—ISOLATED ROD AND CONE VISUAL CELLS OF THE PIG.

a-e, cones; *f-i,* rods, *za,* outer segment; *zi,* inner segment of the cone, the latter consisting of an ellipsoid, *ze,* and a more or less elongated neck, *m; zk,* cone nucleus; *cf,* cone fiber; *sa,* outer, and *si* inner segment of the rod; *sk,* rod nucleus; *sf,* rod fiber. (Kölliker.)

The rods have an average length of 60 microns, and an average diameter of 2 microns. Of the entire extent, the outer cylindric segment and the inner spheroidal segment contribute approximately equal portions.

The inner or nucleated portion of each rod, the *rod fiber,* is found in the outer nuclear layer and is continued as a fine filament, which, having penetrated the external limiting membrane, extends as far as the border line between the outer nuclear and outer reticular layers, at which level the rod filament ends in a knob-like expansion. Similar knobs may appear along its course. At some point in its course through the nuclear layer the rod fiber presents a nucleated enlargement, which, under some conditions, shows one to three alternate light and dark transverse striations, the optical expression of the distribution of the chromatin in the form of bands. The nuclei of the rod fibers are placed at various levels in the nuclear layer, and collectively occupy nearly its entire thickness. Its outer border, however, contains relatively few rod nuclei.

The Cones.—The cones resemble the rods in structure, but their cytoplasmic portion is shorter, the inner segment of which is several times as broad ($35 \, \mu$ by $7 \, \mu$). The outer anisotropic segment is especially short and does not contain

visual purple, which the isotropic basal segment, whose fibrillated ellipsoid occupies a somewhat greater proportion of its length than is the case with the homologous rod segment, rests directly upon, and may even project through the external limiting membrane. The inner or nucleated portion, therefore, begins as a broad nucleated mass, equal in diameter and continuous with the bacillary portion of the cone element, to which it is ofttimes united by a slightly constricted neck. In this inner portion, just within the external limiting membrane, is the cone nucleus; it differs from the rod nucleus in that it stains less deeply, presents no transverse striations, and frequently incloses a distinct nucleolus. From its nucleated portion the *cone fiber* is continued as a rather broad cytoplasmic filament straight inward to the border of the nuclear layer, where it terminates in an expanded portion or *cone foot*, from the flattened inner surface of which the fine filaments penetrate the margin of the outer reticular layer.

The outer segments of both rods and cones are embedded in the cells of the pigment layer, whose delicate filamentous processes project between the rods and cones, frequently extending almost to the external limiting membrane. Both rods and cones are hexagonal or nearly circular in transection. The slight intervals between the neighboring elements and the processes of the pigment epithelium are occupied by a homogeneous fluid, probably a somewhat modified lymph. The rods far outnumber the cones; three to four rods generally appear between two successive cones. The total number of cones in the human retina has been estimated at 7,000,000; that of rods at 130,000,000.

FIG. 563.—DIAGRAM OF THE ROD AND CONE VISUAL CELLS, AND THEIR RESPECTIVE BIPOLAR NEURONS (Schwalbe.)

m.l.e., external limiting membrane; *n.l.e.*, external nuclear layer, *r.l.e.* external reticular (molecular) layer; *n.l.i*, internal nuclear layer (layer of rod and cone bipolars).

External Limiting Membrane.—The external limiting membrane (*membrana limitans externa*) consists of the flattened and amalgamated extremities of the sustentacular cells (*Müller's fibers*), which form the chief supporting tissue, the neuroglia elements, of the retina, and which extend from the extreme inner surface outward to the external limiting membrane. It will therefore be more con-

venient to defer further description of this membrane until the remaining layers have been described, and the müllerian fibers can be considered in their entirety.

FIG. 564.

FIG. 565.

FIG 564—A ROD AND A CONE VISUAL CELL FROM THE FUNDUS OF THE HUMAN RETINA, OUTSIDE THE MACULA LUTEA.

a, outer segment; *b*, inner segment; *c*, rod- or cone-fiber; *d*, nucleus; *e*, rod- or cone-foot; *f*, ellipsoid; *g*, myoid (of cone); *h*, external limiting membrane. (Schäfer, Greeff.) ×1000.

FIG. 565—TWO CONES FROM THE HUMAN RETINA

A, from close to the ora serrata; *B*, from near the margin of fovea centralis. The fiber (*f*) is cut short beyond the nucleus Between the ora and the fovea cones of intermediate lengths are found, forming a series from *A* to *B*. In the central part of the fovea, the cones are still longer than *B*, the increase being due mainly to an elongation of the outer segments (*o.s.*) to about twice the length in *B* (Greeff.) ×1000.

Outer Nuclear Layer.—The outer nuclear layer (*outer granular layer*) consists, for the most part, of the nucleated portions of the rod and cone elements. The outermost zone of this layer contains only cone nuclei; the inner portion, comprising about three-fourths of its thickness, contains only rod nuclei. The

former, with occasional exceptions (Stöhr), are situated in only one relatively narrow plane; the latter are distributed at various levels, though they occur more abundantly in the midregion of the nuclear layer. In addition to portions of Müller's fibers which serve for the support of the nucleated elements, this layer contains the terminal filaments of the distal processes of some of the small bipolar nerve cells of the inner nuclear layer.

Fiber Layer of Henle.—The fiber layer of Henle is formed by that portion of the cone fibers which is internal to the layer of rod nuclei. It is a thin layer and only acquires importance in the neighborhood of the macula lutea, where

FIG 566.—FROM THE HUMAN RETINA

1, outer nuclear layer; *2*, outer reticular layer; *3*, inner nuclear layer; *4*, inner reticular layer; *a*, external limiting membrane; *b*, rod cell nuclei; *c*, cone cell nuclei; *d*, cone bipolars; *e*, rod bipolars; *f*, an exceptionally long process of a rod bipolar. Methylene blue. Highly magnified (Dogiel.)

the cones are most abundant. In this portion of the retina it is easily distinguished from the outer reticular layer by the somewhat radial disposition of its fibers, the fibers of the reticular layer having an irregularly meridional direction.

Outer Reticular Layer.—The outer reticular layer (*outer molecular layer, outer plexiform layer*) presents a dense tangle of neural tissues consisting of supporting neuroglia fibers and interlacing processes from the horizontal and bipolar nerve cells of the inner nuclear layer. Terminal fibrils from this network

venient to defer further description of this membrane until the remaining layers
have been described, and the müllerian fibers can be considered in their entirety.

FIG. 564.   FIG. 565.

FIG. 564.—A ROD AND A CONE VISUAL CELL FROM THE FUNDUS OF THE HUMAN RETINA,
OUTSIDE THE MACULA LUTEA.

a, outer segment; b, inner segment; c, rod- or cone-fiber; d, nucleus; e, rod- or cone-foot;
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about twice the length in *B*. (Greeff.) ×1000

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sists, for the most part, of the nucleated portions of the rod and cone elements.
The outermost zone of this layer contains only cone nuclei; the inner portion,
comprising about three-fourths of its thickness, contains only rod nuclei. The

smaller cells, terminate in the outer reticular layer, probably serving the purpose of association neurons.

Middle Nerve Cells.—The nerve cells of the middle type are usually of bipolar form, and are the most abundant elements of the inner nuclear layer. The one set of their processes is directed outward (peripheralward) ; they pass to the outer
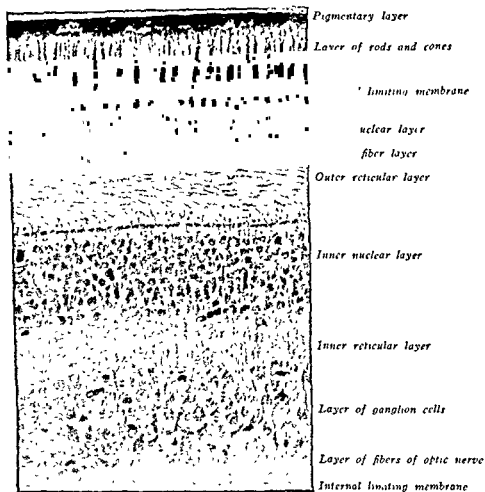
FIG. 568.—VERTICAL SECTION OF HUMAN RETINA (Bausch and Lomb Optical Company.)

reticular layer where they eventually come into relation with either the rod fibers or the cone fibers. Hence those cells which are in relation with the visual rods are classified as *rod bipolars*, those in relation with the visual cones as *cone bipolars* (Fig. 567). The terminal fibrils of the cone bipolars are horizontally, those of the rod bipolars radially, disposed.

The central processes, axons, of the bipolar cells are directed inward (centralward), and on entering the inner reticular layer terminate in an end brush which is in relation with the dendritic processes from the large ganglion cell layer.

Inner Nerve Cells.—The inner nerve cell type (*amacrine cells of Cajal*) are large nerve cells which occupy a narrow zone at the inner margin of this nuclear layer. These are large stellate cells whose dendritic processes extend into the

intermingle in the fiber layer of Henle with terminal fibrils from the cone feet; more externally they are in intimate relation with the end-knobs of the rod fibers. This arrangement permits the transmission of stimuli from the neuro-epithelium to the retinal ganglion.

Inner Nuclear Layer.—The inner nuclear layer (*inner granular layer, ganglion retinae, outer ganglionic layer*) contains a mass of nerve cells, together with the nucleated portion of the sustentacular fiber cells of Müller. The nerve cells may be described as corresponding to one of *three types*, which, from the plane in which they are distributed may be termed the outer, middle, and inner.
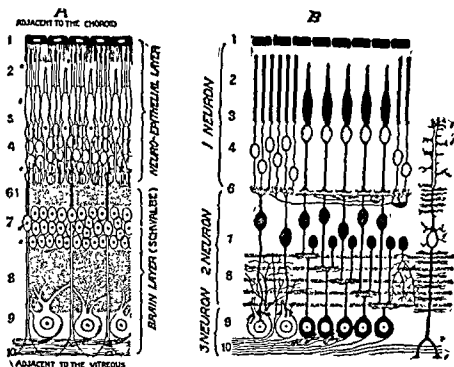
FIG. 567.—DIAGRAMS OF THE HUMAN RETINA, SHOWING THE RELATIONSHIPS TO EACH OTHER OF THE RETINAL NEURONS, AND THEIR DISPOSITION IN THE DIFFERENT LAYERS.

(From Fox, *Ophthalmology*.)

Outer Nerve Cells.—The outer nerve cells (*horizontal cells, basal cells*) possess pyramidal, stellate, or flattened cell bodies whose dendrons are distributed to the horizontal plexus of the outer reticular layer. These cells vary in size; the dendritic or distal processes of the smaller cells on reaching Henle's layer are in relation with the terminal fibrils of the cone feet; those from the larger nerve cells are in relation with the terminal knobs of the rod fibers. The axis cylinders or central processes from all these cells after traveling horizontally—*viz.*, in a plane parallel to the layers of the retina—for a greater or less distance, turn inward and pass to the inner reticular layer, where they come into relation with the dendrons of the large nerve cells of the ganglion cell layer. Other processes, mostly from the

neurospongium. To these are added a much branched portion of Müller's fibers, which form the chief supporting tissue of this layer. The cell processes entering into this formation are derived from the cells of the inner nuclear and ganglion cell layers, and it is here that the processes of these cells interlace so closely as to permit the transmission of impulses from the one neuron to the other. Their terminal arborizations are, for the most part, disposed in horizontal planes, though a few spread throughout the entire thickness of the reticular layer.

Ganglion Cell Layer.—The ganglion cell layer (*ganglion nervi optici, inner ganglionic layer, layer of large nerve cells*) is of variable thickness. Its greatest depth is in the region of the macula lutea, where it consists of five or six superposed ganglion cells. Toward the equator of the eye it becomes progressively thinner, until near the ora serrata its single layer of cells only forms an incomplete stratum

The cells comprising this layer are mostly large, stellae, pyriform, or spheroidal nerve cells, from whose peripheral border dendrons pass to the inner reticular layer, and from whose central border an axon passes to the nerve fiber layer to eventually become the axis cylinder of a fiber of the optic nerve.

These cells, though varying much in size and shape, possess a body of the usual structure with neurofibrils and chromophilic granules, and a pale vesicular nucleus with a distinct chromatic nucleolus. Intermingled with the nerve cells are many fine branches of the sustentacular cells which here form an open-meshed network within whose spaces the nerve cells are inclosed.

FIG 571.—A NERVE CELL OF THE LARGE GANGLION CELL LAYER; FROM THE RETINA OF A CAT.

n, n, axon; *c, c,* collaterals Golgi's stain. ×325. (Kolliker)

Nerve Fiber Layer.—The nerve fiber layer, in intimate relation to the preceding, forms the innermost of the retinal zones. It consists of naked axis-cylinders passing from their origin in the ganglionic layers to their immediate destination, the optic nerve. They are, therefore, mostly if not wholly centripetal fibers. A few centrifugal fibers have been demonstrated in this layer, but they would appear to be probably vasomotor in function, a few possibly ending in relation to the amacrine cells.

The nerve fibers of this layer converge from all portions of the retina, follow a meridional course through the open meshes of the network of branching sustentacular cells, and converge toward the optic papilla, the entrance, or rather the point of exit, of the optic nerve Hence the nerve fiber layer, being augmented by the constant acquisition of new axons from the ganglion cells, becomes pro-

inner reticular layer and take part in the formation of the dense feltwork of which that layer consists. The course of the axis-cylinders of these cells is still a matter of some doubt. Ramón y Cajal, believing these cells to possess no axon, designated them "amacrine cells" and subdivided them according as their dendrons were dis-
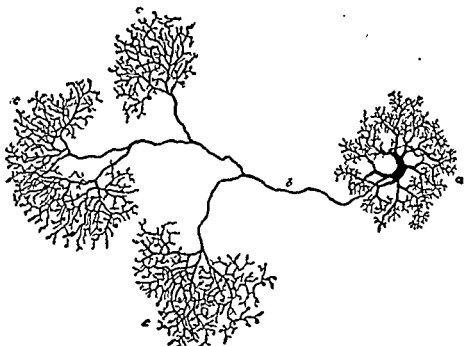
FIG. 569.—HORIZONTAL CELL FROM THE RETINA OF A CALF.

a, cell body; *b*, axon; *c*, terminal arborizations of the axon. Golgi's stain ×150. (Marenghi.)

tributed in either one of several horizontal planes (the number varying in different species) or diffusely throughout the inner reticular layer.

Some of the amacrine cells, however, send an axon in a horizontal direction to the inner reticular layer, and are also in relation with the terminal arborizations

FIG 570.—TWO AMACRINE CELLS FROM A TRANSECTION OF THE RETINA OF A CALF. Golgi's stain. ×260. (Kolliker.)

of centrifugal nerve fibers which enter from the nerve fiber layer. These have been regarded by some observers as dislocated nerve cells of the ganglion cell layer; Cajal named them "association amacrins."

Inner Reticular Layer.—The inner reticular layer (*inner molecular layer, inner plexiform layer*) is a densely tangled network of nerve-cell processes, a

stance is somewhat thickened; it sends off fewer but coarser lateral processes, and in the midregion of this layer presents an enlargement which is almost entirely occupied by the large ovoid nucleus.

The fiber cell, somewhat narrowed, may then be traced through the outer reticular to the outer nuclear layer, where its processes form a dense network about the nucleated segments of the rod and cone visual cells.

The terminal processes of the fiber cells become again flattened, somewhat after the manner in which the internal limiting membrane is formed, and are so closely approximated as to form an *external limiting membrane*, a distinctly membranous structure which derives a reticular appearance from being pierced by each of the innumerable rod and cone elements.

From the outer surface of the expanded ends of the mullerian fiber cells which form the external limiting membrane, minute fibrils are continued between the bases of the non-nucleated portions of the rod and cone cells to form shallow sockets, the *rod and cone sockets*, into which the bacillary portions of these elements are fixed. The neuroglia supporting tissue includes also the ordinary long- and short-rayed astrocytes, limited, however, to the cerebral portion of the retina.

The Macula Lutea (Yellow Spot)

The macula lutea being apparently the most highly developed portion of the retina, deserves some special consideration. The macula is a circular elevation about 2 millimeters in diameter, in the center of which is a marked depression, the *fovea centralis*. It is yellow in color, due to the presence of a pigment. The elevation results from an increased thickness of all the retinal layers, but especially of the ganglion cell layer, which in this portion of the retina is five or six cells deep. The reticular layers are also much thickened in this area. In the bacillary
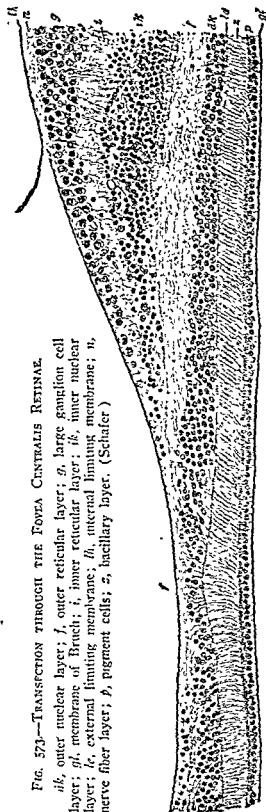
FIG. 573.—TRANSECTION THROUGH THE FOVEA CENTRALIS RETINÆ.

nk, outer nuclear layer; *l*, outer reticular layer; *o*, large ganglion cell layer; *pl*, membrane of Bruch; *i*, inner reticular layer; *ik*, inner nuclear layer; *ic*, external limiting membrane; *lh*, internal limiting membrane; *n*, nerve fiber layer; *p*, pigment cells; *z*, bacillary layer. (Schafer.)

gressively thicker toward the posterior pole of the eye, and is thickest at the margin of the optic papilla, where it is so highly developed as to almost exclude the other retinal layers.

The course of these unmyelinated nerve fibers is not straight; on the contrary, they interlace to form a delicate fibrillar network. At the margin of the papilla optica the nerve fibers bend outward with a sharp curve almost at right angles

to their former course. At this point also they gradually acquire a myelin sheath and, uniting into many bundles, penetrate the numerous openings of the lamina cribrosa of the sclerotic and choroid coats to form the optic nerve.

Supporting Tissues of the Retina

These consist of a gliaform reticulum distributed throughout the cerebral portion of the retina, and of a special supporting tissue, Müller's fibers, which may also be regarded as glia tissue, though they are common to both the neural and epithelial portions.

Fibers of Müller.—The fibers of Müller (*radial fibers; sustentacular cells*) comprise numerous large glia cells whose processes begin with an expanded base at the inner surface of the nerve fiber layer, and can be traced all the way through the retina to the membrana limitans externa, which is likewise formed by the terminal expansions of these cells. The nucleus of the fiber cell lies in the midregion of the inner nuclear layer.

The expanded and flattened bases or inner extremities of these glia cells are so closely approximated to one another as to form a complete investment for the inner surface of the retina, which is known as the *internal limiting membrane (membrana limitans interna)* and is frequently classed as the innermost layer of the retina. Under low magnification it appears as a continuous membrane, but under higher powers it is readily resolved into the broad, conical, basal expansions of which it consists From these initial expansions the glia cells may be traced outward through the nerve fiber and ganglion cell layers by means of the numerous coarse processes or glia fibers.

FIG. 572—A FIBER CELL OF MÜLLER, OR SUSTENTACULAR CELL, FROM THE DOG'S RETINA

1, nerve fiber layer; *2*, ganglion cell layer; *3*, inner reticular layer; *4*, inner nuclear layer, *5*, outer reticular layer; *6*, outer nuclear layer; *a*, a process extending into the inner reticular layer; *b*, nucleus of the cell; *m l e.*, external limiting membrane; *m l i*, internal limiting membrane Golgi's stain Highly magnified. (Cajal.)

The glia fibers then pass in a fairly straight course through the inner reticular layer. In this portion numerous short, fine, lateral offshoots from the main stem support the neurospongium of the reticular layer. Continuing through the inner nuclear layer the glia sub-

The visual purple is said to be absent in the eyes of the pigeon, the hen, some reptiles and some bats. It is supposed to enhance the irritability of the rods in dim lights.

In the eyes of birds and reptiles the cones outnumber the rods; and in certain reptiles, *e.g.*, lizards, rods are entirely lacking. In sharks and rays, most nocturnal animals, the owl, and the bat, cones are either absent or few in number or rudimentary in structure. In the mouse and the cat the rods greatly predominate.
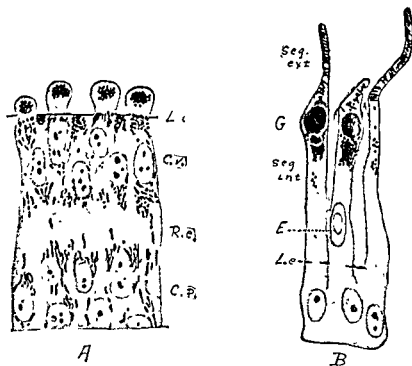
FIG. 575—TWO EARLY STAGES IN THE DEVELOPMENT OF THE ROD AND CONE VISUAL CELLS IN THE CHICK.

A, from twelve-day embryo, showing the visual cell buds containing mitochondria; *L.e*, external limiting membrane, *C V*, visual cell, *R e*, external reticular layer; *C.p.*, bipolar cells; *B*, from one-day-old chick, showing two complete rods and one cone, both elements containing a large lipoid spherule (*G*) and mitochondria. The cone contains an ellipsoid (*E*); *seg. int.*, internal segment, *seg ext*, external segment (Leplat.) × about 2000.

According to the view of Kreis (1895) the cones function in the perception of color in strong light, the rods are sensitive only to light and darkness. In color blindness the cones are defective, in night blindness the rods are affected.

Night blindness results from an absence of vitamin A. The visual purple of the rod elements of the retina is the product of the combination of vitamin A with protein, forming a conjugated carotenoid protein, the *rhodopsin* or *retinene*. Vitamin A enters also into the chemical cycle of cone vision, forming a cone sensitive substance, the so-called visual violet or *iodopsin*.

Development of Rods and Cones.—The rods and cones arise and by an essentially identical mode of differentiation from apparently similar embryonic cells.

layer, within the area of the macula, the cones are far more numerous than elsewhere, especially when considered in relation to the rods, which are greatly diminished peripherally and absent centrally. The cones of the macula are almost twice as long as those of the equatorial region of the retina, the increased length being due to elongation both of the internal and external segments, but mainly the latter. They are also somewhat more slender, and their nuclei may be placed some distance beyond the external limiting membrane.

Toward the *fovea centralis* the inner layers of the retina become very much thinned, until at its center the nerve tissues are merely represented by scattered
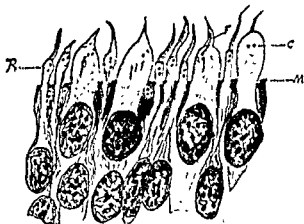
FIG. 574.—DEVELOPING ROD AND CONE VISUAL CELLS, FROM THE RETINA OF A 345 MILLIMETER (SIX MONTHS) HUMAN FETUS.

M, diplosome in a Muller's fiber at the level of the external limiting membrane; C, diplosome in a cone cell; F, fiber growing out from the cone diplosome; R, diplosome in a rod visual cell. (Seefelder.) ×1000.

cells of the inner nuclear and ganglion cell layers. Rod elements are not found in this area; the bacillary layer consists entirely of elongated, slender cones, from 2 to 4 microns in diameter and from 70 to 80 microns in length. The much elongated nuclear portion of the cones deviates in a slanting direction toward the margin of the macula, and the cone nuclei are further removed from the external limiting membrane than elsewhere in the retina.

The pigment of the epithelial layer is much diminished and may even be absent at the fovea. Because of the diminution in the number of ganglion cells in this area the nerve fiber layer is greatly diminished in thickness on approaching the margin of the fovea, and toward its center entirely disappears.

The fovea centralis lies at the posterior pole of the anteroposterior axis. The light stimulus here meets least obstruction in passing to the neuro-epithelial elements, the photoreceptors, thus is the point of acutest vision. The fovea has a diameter of about 0.4 millimeter.

Since the fovea centralis contains no rods, it lacks the visual purple; and since vision is sharpest at this point, the visual purple would seem unessential to sight.

is appropriately described as an inverted sense organ. The most plausible theory yet proposed in explanation of this inversion of the visual cells seems to be the one outlined by Balfour (1881), expressed in terms of the ancestral history of the vertebrate eye. (Among the invertebrates an inverted retina is known only in certain mollusca, *e.g.*, Pecten, and in certain spiders and the scorpion.)

According to this view the vertebrate retina originated on the outer surface of the ancestral vertebrate in much the way that the eyes of many invertebrates have been produced. The primitive retinas thus formed were implanted in that portion of the surface of the animal from which the central nervous system was destined to develop, and when this was infolded these retinas were carried in with it and came thus to be involved in the central organ. If the morphological position of a sensory cell, such as may have existed in the primitive external retina, is supposed to have been thus retained as this organ was carried from its superficial location into the central nervous system and out again almost to the external surface, the resulting retina would be composed of inverted elements (Fig. 576). Thus this theory at once offers an explanation for the two most striking features of the vertebrate retina, namely, its formation as an apparent outgrowth from the central nervous system and the inverted condition of its receptive cells.

The difficulties of this theory are discussed, and an alternative theory, based upon the direction eyes of Amphioxus, is presented by Parker.[8]

The Optic Nerve

The optic nerve is a large nerve trunk, composed, like the white matter of the brain of which it is an ontogenetic portion, of myelinated nerve fibers without a neurilemma, supported by a neuroglial network containing long-rayed fibrous astrocytes. It receives an investing sheath from each of the cerebral membranes, septa from the pia mater enveloping the several funiculi. These sheaths are continued as far forward as the eyeball, at which point they become continuous with the sclera. Though the choroid corresponds to the pia mater, the two are not apparently in direct continuity. It has been estimated that each optic nerve contains about half a million fibers; a number equal to that of all the fibers which enter the spinal cord by the posterior roots from the whole of the body (Starling).

Lying in the axis of the nerve, the *arteria centralis retinae* with its accompanying vein enters the eye and appears on the inner surface of the retina at the *porus opticus* (physiologic excavation, *optic disk*) in the center of the *optic papilla*. Here it divides, its two branches at first pursuing a meridional course between the hyaloid membrane and the retinal surface; soon they pierce the latter to supply the cerebral (neural) portion of the retina. No vessels penetrate the neuroepithelial portion of the retinal layers; these are nourished by the choroid. The *vena centralis retinae* pursues a course like that of the artery.

[8] Parker, 1908.

A protoplasmic bud is pushed beyond the external limiting membrane towards the layer of pigmented cells. The cone bud is from four to five times as stout as that of the rod cell. These processes carry apically a diplosome, surrounded by a lighter cytoplasmic halo. From each member of the diplosome a fiber-process grows out, one passing towards the elongating distal, the other towards the proximal, pole of the cell. The distal process thus becomes enveloped by an extension of the cell cytoplasm, the two constituents, fiber and investing cytoplasm, uniting in the formation of the outer segment of the rods and cones. Seefelder [6] has confirmed the essential points in the earlier descriptions of rod
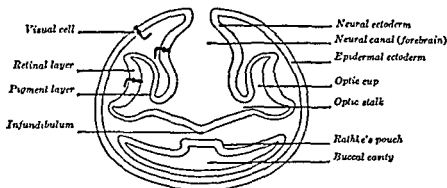
FIG. 576.—DIAGRAM ILLUSTRATING BALFOUR'S THEORY TO ACCOUNT FOR THE INVERSION OF THE VISUAL CELLS OF THE VERTEBRATE RETINA.

Transverse section through the head of a hypothetical vertebrate embryo, to show the morphological relations of the surfaces of the ectoderm of the integument, the neural tube, and the forming retina. In each of these situations a single sense cell is indicated. (Parker.)

and cone differentiation by Leboucq (1909) and by Magiott (1910). Leplat [7] has investigated the rôle of the mitochondria in connection with this process. He describes the migration of the plastosomes into the external segment where they become chemically altered and disappear as such in their contribution to the homogeneous cytoplasmic sheath of the centrosomal filament of the external segment. Leplat inclines to regard the transverse striation of this segment and its cleavage into disks by maceration as the expression of its mode of construction from mitochondria. It remains uncertain whether the longitudinal fibrillation of the internal segments is likewise the probable result of an arrangement of mitochondria in the developing cell; the complete history of these mitochondria has not yet been traced.

Inversion of the Retina.—The receptive cells of the vertebrate retina exhibit, in contrast to all other neuro-epithelial cells, a reversed polarity with respect to the source of their special stimulus, the light waves; the transmitting end of the cells is nearer the source of the light than the percipient end. The human retina

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[6] Seefelder, 1914.
[7] Leplat, 1913.

Crystalline Lens.—The crystalline lens with its suspensory ligament forms a sort of diaphragm which separates the ocular cavity into two compartments, of which the anterior is occupied by the aqueous humor, the posterior by the vitreous humor.

The lens is a biconvex transparent body having a somewhat greater convexity on its posterior than on its anterior surface; its curvature is greater at its margin than toward its center. It has a transverse diameter of from 8 to 9 millimeters, and an anteroposterior diameter of from 3.5 to 4 millimeters according to the degree of accommodation. It consists of a capsule, epithelium and a substantia lentis.

Capsule.—The capsule of the lens is a homogeneous membrane which covers its entire surface and receives the attachment of the suspensory ligament. It presents faint meridional striations and may sometimes be separated into several lamellae. This lamellation may be purely artificial, but appears to be somewhat dependent upon the attachment of the fibers of the suspensory ligament to the surface of the lenticular capsule.

The capsule is about twice as thick over the anterior as over the posterior surface of the lens On the former surface it is in relation with the lenticular epithelium, but on the posterior surface the capsule rests directly upon the substantia lentis The anterior surface of the capsule is in gentle contact with the free margin of the iris.

Epithelium.—The lenticular epithelium consists of a single layer of cells which covers the entire anterior convexity of the lens, extending as far back as its equator The height of these cells varies with the age of the individual. In fetal life they are distinctly columnar, in youth short columnar or cuboidal, in adult life low cuboidal or flattened. Toward the margin of the lens the epithelial cells become progressively lengthened, and at its equator are transformed directly into the fibers of the lenticular substance. This definitive structure of the lens recalls its manner of development from the original lens vesicle; the hollow vesicle becomes solid by the elongation of the cells of the posterial wall.

FIG 578—LENS FIBERS

1, in profile, from the crystalline lens of the ox's eye; *2*, in transection, from the human crystalline lens. ×350. (Kölliker)

*Substantia Lentis —*The substantia lentis is, therefore, the product of the epithelium of the lens, whose cells become greatly elongated to form slender hexagonal prisms, known as the lens fibers When it is first formed each prism exhibits a nucleus which persists for some time, but gradually disappears as in the process of growth the older fibers become farther and farther removed from their source of nutrition, the lymph and the aqueous humor in which the surface

The Ora Serrata

At the ora serrata (Fig. 550) the typical layers of the retina, already much thinned, abruptly cease. The first elements to disappear are the rods and cones. The cones, which become much shorter, and practically lack the outer segment, extend farther toward the ora than the rods. The remaining layers are continued forward only as the double layer of epithelial cells belonging to the pars ciliaris retinae, the inner stratum of which appears to be analogous to and continuous with the cerebral portion of the retina, apparently the sustentacular cells; while the outer, deeply pigmented layer apparently represents the pigmented layer of the retina. For some distance toward the ora serrata, the retina becomes modified by the presence of large vacuoles, probably lymph spaces.

THE OCULAR CONTENTS

Within the ocular globe, whose walls are formed by the three coats of the eye, are certain structures which may be collectively considered as its contents. They are: aqueous humor, crystalline lens, vitreous humor, hyaloid membrane and suspensory ligament.

Aqueous Humor.—The aqueous humor is a fluid, closely allied to lymph, which occupies the anterior and posterior chambers of the eye. Microscopically it is structureless. Occasional leukocytes, migrants from adjacent lymph channels, may be encountered. It is in virtual equilibrium with the cerebrospinal fluid and the blood plasma. It is more intimately related to the venous pressure, being only slightly affected by changes in the arterial pressure.[9]
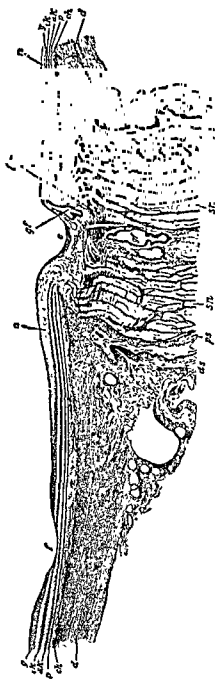
FIG. 577.—ENTRANCE OF THE OPTIC NERVE.

ab, outer granular layer of the retina; ch, choroid coat; d, sclera; ds, dural sheath; c, depressed center of the optic papilla; f, fovea centralis; g, layer of ganglion cells; gf, blood vessels; ik, inner granular layer; lcr, lamina cribrosa; n, nerve fiber layer; p, pigment layer; ps, pial sheath; sn, funiculi of optic nerve fibers. X17. (Kölliker.)

and varicose processes, have been demonstrated in small numbers within the vitreous body. Small rounded cells somewhat resembling leukocytes are also found, but for the most part they are flattened against the hyaloid membrane. They occur in very limited numbers.

These various cells, as well as occasional filamentous remnants of the original mesenchymal constituents of the vitreous humor, may cast shadows upon the retina within the visual field. Such shadows, called *muscae volitantes*, on account of their flitting motion when the eyes are moved, are seen when looking at a

FIG 579.—THE NUCLEAR ZONE AT THE MARGIN OF THE CRYSTALLINE LENS OF A CHILD'S EYE, SHOWING THE TRANSITION OF THE LENS EPITHELIUM TO THE LENS FIBERS AND THE ATTACHMENT OF THE SUSPENSORY LIGAMENT

a, lens fibers; *b*, lenticular epithelium; *c*, capsule of the lens; *d*, suspensory ligament. ×273

bright light, or frequently in looking through the microscope. In advanced age crystals may form in the vitreous which are observed to settle to the bottom of the eye when the eyes are held still.

Hyaloid Membrane.—The hyaloid membrane is a very thin structure which surrounds the vitreous humor and unites it to the inner surface of the retina and the crystalline lens. It consists of delicate glassy fibers so disposed as to

of the lens is bathed. This change is accompanied by a hardening or cornification and slight shrinkage of the lens fibers, so that those prisms which come to occupy the center of the lens form a dense, hard mass of non-nucleated fibrous cells with faintly serrated margins. The peripheral fibers retain their smooth edges and their nuclei, and form a protoplasmic mass of much softer consistency. The hardened central mass is the so-called *nucleus of the lens*. Any opacity of the lens or its capsule is known as a cataract.

The nuclei of the lens fibers remain in the neighborhood of the equator, where they are first formed, and are thus contained within a narrow, superficial, equatorial zone, the *nuclear zone*.

Each lens fiber is disposed along a meridian of the lens, and extends from its anterior to its posterior hemisphere. The fibers are so arranged that they abut upon one another, end to end, along V-shaped lines which radiate from either pole. This union is often quite firm, and thus are formed long fibrous bands which can be traced from the anterior to the posterior hemispheres along the lens. These bands are distributed in a peculiar manner. Near each pole along the line of abutment, the band may be said to bend upon itself with a sharp curve—making an angle of about 60 degrees—whose convexity is directed toward the pole, the parallel fibers being so arranged as to form a sector whose apex is also directed toward the pole. The corresponding sectors of opposite poles overlap one another so that the fibrous bands are continued from one side of one polar mass to the reverse side of the overlapping sector and so back, on the farther side, to the adjacent sector of the former hemisphere. By teasing, fibrous bands can sometimes be traced successively through all of the polar sectors and thus back to a sector beneath that from which the start was made. Obviously no individual lens fiber is of sufficient length to extend from pole to pole of the lens

The polar figures formed by the lines of terminal union of the lens fibers are known as *lens stars*. These are at first three-rayed, but later become six- and even nine-rayed.

During the earlier stages of the development the lens is invested by a delicate vascular membrane, the tunica vasculosa lentis (designated pupillary membrane in front), supplied by the hyaloid artery continued from the central artery of the retina. This tunic normally disappears before birth. Its atypical persistence in whole or in part seriously interferes with vision.

Vitreous Humor.—The vitreous humor (*vitreous body*) is a soft jelly-like mass which fills the entire cavity of the eye behind the line of the ora serrata and crystalline lens. About 98 per cent of its composition is water. It is completely invested by the hyaloid membrane. Its anterior excavation which holds the posterior convexity of the lens is known as the *hyaloid* or *patellar fossa*. The vitreous humor appears to be a peculiarly delicate form of very loose gelatinous connective tissue whose scanty fibers present a somewhat concentrically lamellated arrangement and are so very delicate as to be recognized under ordinary conditions only with the greatest difficulty.

Occasionally stellate and fusiform cells, remarkable for their large vacuoles

and varicose processes, have been demonstrated in small numbers within the vitreous body. Small rounded cells somewhat resembling leukocytes are also found, but for the most part they are flattened against the hyaloid membrane. They occur in very limited numbers.

These various cells, as well as occasional filamentous remnants of the original mesenchymal constituents of the vitreous humor, may cast shadows upon the retina within the visual field Such shadows, called *muscae volitantes*, on account of their flitting motion when the eyes are moved, are seen when looking at a

FIG. 579—THE NUCLEAR ZONE AT THE MARGIN OF THE CRYSTALLINE LENS OF A CHILD'S EYE, SHOWING THE TRANSITION OF THE LENS EPITHELIUM TO THE LENS FIBERS AND THE ATTACHMENT OF THE SUSPENSORY LIGAMENT

a, lens fibers; *b*, lenticular epithelium; *c*, capsule of the lens; *d*, suspensory ligament. ×273.

bright light, or frequently in looking through the microscope. In advanced age crystals may form in the vitreous which are observed to settle to the bottom of the eye when the eyes are held still.

Hyaloid Membrane.—The hyaloid membrane is a very thin structure which surrounds the vitreous humor and unites it to the inner surface of the retina and the crystalline lens. It consists of delicate glassy fibers so disposed as to

form an extremely thin reticular membrane. It passes forward over the inner surface of the retina, to which it is loosely united, until at the ora serrata its fibers leave the retinal surface and pass inward to the margin of the lens to become inserted into the lenticular capsule.

Suspensory Ligament (Zonula Ciliaris).—Certain fibers from the hyaloid membrane pass forward from the ora serrata and are firmly adherent to the ciliary processes, or become attached in the grooves between the processes. From the sides of these processes fibers diverge at frequent intervals and pass to the margin of the lens, where they are attached on either side of the equator, spreading over a zone which is somewhat narrower posteriorly than anteriorly. These fibers form the suspensory ligament of the crystalline lens (Figs. 556, 579). They occupy an annular zone which is included between the ciliary processes and the margin of the lens, and which is known as the *zonula ciliaris (of Zinn)*.

The glassy fibers of this ligament take origin from the sides of the ciliary processes along which they are firmly attached, becoming free only near the apices of these processes. They pass ,thence to the margin of the lens and spread out upon the surface of the capsule to which they are intimately adherent. The fibers arising more posteriorly are said to be attached to the lens anteriorly to the equator, those arising from the more anterior portions of the ciliary processes becoming attached posteriorly to the equator of the lens.

The most anterior of these fibers form a somewhat plicated but incomplete membrane which serves as the anterior boundary of an annular series of connecting lymphatic spaces collectively forming the *spatia zonularis (canals of Petit)*. This irregularly sacculated, annular canal is bounded posteriorly by the hyaloid membrane, anteriorly by the incomplete membranous wall of the posterior chamber through which ,the aqueous humor readily diffuses, internally by the margin of the crystalline lens, and antero-externally by the ciliary processes. Besides supporting the lens, the suspensory ligament assists in the accommodation of the lens to far and near vision, a process involving a change of convexity, and dependent upon the activity of the ciliary muscle.

BLOOD VESSELS

The circulation of blood in the globe of the eye is maintained through *four sets of vessels:* (1) the arteria and vena centralis retinae, (2) the short ciliary arteries and venae vorticosae, (3) the long ciliary arteries and (4) the anterior ciliary arteries and veins

Arteria Centralis.—The arteria centralis, destined for the supply of the retina, enters the optic nerve about midway between the optic commissure and the ocular globe, and arriving at the center of the nerve runs in its axis to the papilla optica. Here it divides into two branches, an inferior and a superior, which, by rapid dichotomous division, radiate from the optic papilla to all parts of the retinal surface, thereby forming a plexus of small arteries within the nerve fiber and ganglion cell layers. From this plexus capillaries are distributed to all the cerebral

layers of the retina. No blood vessels are found within the neuro-epithelial layers. The retinal arteries, like those of the brain, do not anastomose with one another; they are terminal arteries.

The retinal veins follow the course of the arteries; they converge to form a
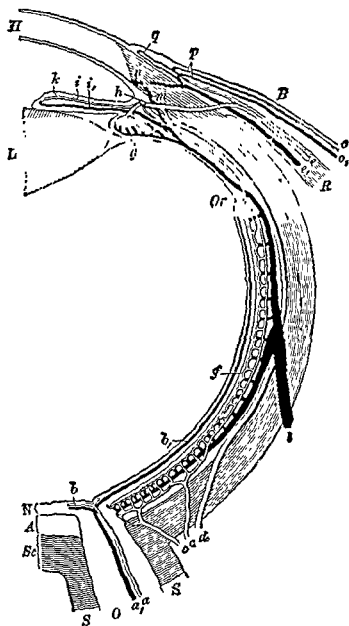
FIG. 580—SCHEMATIC REPRESENTATION OF THE INTRINSIC BLOOD VESSELS OF THE EYE.

Arteries in outline, veins in solid black. *A*, choroid; *a*, central artery, and a_1, vein of the retina; *B*, conjunctiva; *b*, retinal arteries; b_1, retinal veins; *c, c*, short ciliary arteries; *d*, long ciliary artery; *e, e_1*, anterior ciliary arteries and veins; *f*, choriocapillaris; *g*, capillaries of the ciliary body; *H*, cornea; *h*, circulus major of the iridal arteries; *i*, arteries, and i_1, veins of the iris, *k*, circulus minor of the iridal arteries; *L*, crystalline lens; *l*, venae vorticosae; *m*, anastomosis of ciliary and anterior ciliary veins; *N*, retina; *n*, canal of Schlemm; *O*, optic nerve; *o*, posterior conjunctival artery, and o_1, vein; *p*, anterior conjunctival vessels; *q*, vascular loops at the margin of the cornea; *R*, internal rectus muscle; *S*, sheath of the optic nerve; *Sc*, sclera. (Leber.)

single efferent vessel, the vena centralis retinae. The retinal veins are peculiar in that their walls contain no muscle. The optic nerve is supplied with small branches from the arteria and vena centralis retinae in their passage through its substance.

In the fetus a small branch, the *hyaloid artery*, apparently the direct continuation of the arteria centralis retinae, passes forward through the vitreous humor to the posterior surface of the lens, whence capillary vessels pass around the margin of the lens and are connected with the anterior ciliary vessels at the margin of the iris. The hyaloid artery supplies blood to the fetal tunica vasculosa lentis for the nutrition of the developing lens. Before birth these vessels disappear. The hyaloid artery remains for a time as a delicate fibrous strand, occupying the persistent *canalais hyaloideus* or *canal of Stilling*, which lies almost in the visual axis and extends from the papilla optica to the posterior surface of the lens. The hyaloid canal (also called the canal of Cloquet) establishes a channel between the aqueous humor and the lymphatic spaces of the retina. In adult life both the vitreous humor and the crystalline lens are bloodless tissues.

Short Ciliary Arteries.—The short ciliary arteries, twelve to fifteen in number, enter the globe of the eye in a circle (*circle of Zinn*) which surrounds the optic nerve. They supply branches to the meningeal sheaths of the optic nerve and to the sclera, their main stems penetrating this coat to enter the choroid. Here they subdivide to form the plexus of arteries in the lamina vasculosa from which the vessels of the choriocapillaris are supplied. The capillaries of the last-named layer unite to form small venous radicles which converge toward the equator of the eye. Here they unite in a whorl-like manner to form the four or five *venae vorticosae*, which pass obliquely backward through the sclera, receiving additional branches from this coat, and finally emerging from the eye to empty into the ophthalmic vein.

The vessels of the choroid communicate posteriorly with those of the optic nerve, and anteriorly, by a free anastomosis, with those of the ciliary processes.

Long Ciliary Arteries.—The long ciliary arteries, two in number, enter peripherally at the circle of Zinn on either side of the optic nerve, and pass horizontally forward upon the outer surface of the choroid to the ciliary muscle Near the base of the iris they divide, and by anastomosis with each other and with the anterior ciliary arteries form a vascular ring, the *circulus arteriosus iridis major*, about the base of the iris.

From this circle recurrent branches supply the ciliary body and anastomose with the vessels of the choroid; other branches pass into the iris and, converging toward the visual axis form, just outside the pupillary margin, a second annular anastomosis, the *circulus minor*.

The veins of the iris and ciliary body follow closely the distribution of the arteries, the greater portion of their blood returning through the veins of the choroid and the venae vorticosae. Some, however, is returned by means of anastomoses with the anterior ciliary veins.

Anterior Ciliary Arteries.—The anterior ciliary arteries, eight in number, and derived from the muscular and lacrimal branches of the ophthalmic, distribute

branches to the conjunctiva and sclera. Within the sclera, about 2 millimeters outside of the corneal margin, they pass to the circulus iridis major and partially supply the iris and ciliary body as already described.

The anterior ciliary veins follow the course of the corresponding arteries. They empty into the vessels of the ocular conjunctiva.

THE LYMPHATIC SYSTEMS

The lymphatic systems of the eye include very few true lymphatic vessels, but consist rather of a series of channels which may be arbitrarily considered as an anterior and a posterior set of intercommunicating spaces. The former set includes the lymphatic spaces of the cornea, the spaces of Fontana, the anterior and posterior chambers, the lymphatic clefts of the ciliary muscle and iris, and the zonular spaces or canals of Petit. The posterior set includes the subdural and subarachnoid spaces in the sheath of the optic nerve, the capsule of Tenon, the lymphatic spaces of the lamina suprachoroidea, the perivascular spaces of the choroid and retina, the irregular clefts between the pigmentary and bacillary layers of the retina, the similar clefts of the ganglion cell layer, the lymphatic spaces of the hyaloid membrane, the hyaloid canal, and the interstices of the vitreous humor.

These two sets of lymphatic channels communicate with each other by means of the perivascular spaces of the two outer tunics, as well as through that portion of the hyaloid membrane which forms the posterior wall of the spatia zonularis, through the clefts of which and the hyaloid canal the lymph of the vitreous body communicates freely with the aqueous humor of the spatia zonularis and posterior chamber. Consequently, if the cornea be penetrated either accidentally or otherwise, and the anterior and posterior chambers be emptied, their aqueous humor is rapidly replaced, not only from the adjacent spaces of the anterior set of lymphatic vessels, but from the vitreous humor and posterior set as well.

It is also important to note that the posterior set of lymphatic spaces is directly connected through the meningeal sheaths of the optic nerve with the subdural and subarachnoid spaces of the cerebral meninges.

NERVES

The nerves of the eye, in addition to the optic, are the long and short ciliary branches of the ophthalmic nerve. The former, two or three in number, and the latter, six to ten, after supplying a vasomotor branch to the arteria centralis retinae, pierce the sclera in company with the corresponding ciliary arteries and pass meridionally forward on the inner surface of the sclera. Here they supply branches to this tunic and to the vessels of the choroid, and finally reaching the ciliary muscle, their branches form an annular plexus containing a few ganglion cells.

From this plexus fibrils are supplied to the blood vessels and muscular tissues

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Anterior Ciliary Arteries.—The anterior ciliary arteries, eight in number, and derived from the muscular and lacrimal branches of the ophthalmic, distribute

fatty degeneration and is similar in structure to the saccules of the ordinary
sebaceous glands. The glands are embedded in the connective tissue of the con-
junctiva and are so large as to form projecting ridges on its surface, which are
disposed in vertical lines radiating from the row of glandular orifices at the margin

FIG. 581.—VERTICAL SECTION THROUGH THE UPPER EYELID

a, sweat glands; *a1*, primary tarsal arch; *as*, secondary tarsal arch; *b*, conjunctival epi-
thelium; *c*, eyelashes, *co*, rugated portion of the conjunctiva; *d*, epidermis, *e*, fine hairs, *f*,
process of the levator palpebrae superioris which is inserted into the skin, *g*, meibomian gland;
h, internal angle of the margin of the lid; *l*, levator palpebrae superioris, *m*, duct of a meibomian
gland; *o*, orbicularis palpebrarum muscle; *p*, superior palpebral muscle of Müller; *r*, ciliary
muscle of Riolan; *s*, glands of Moll; *t*, fibrous tissue of the tarsus, *v*, external angle of the
margin of the lid; *w*, posterior tarsal glands, *z*, sebaceous glands (Fuchs)

of the lid. At their blind extremities the glands are often slightly *bent or curved*
upon themselves, and this portion is embedded in a dense mass of fibrous tissue
known as the *tarsus.*

The tarsus in each eyelid forms a compact plate-like mass of areolar con-
nective tissue which is so dense and resistant as erroneously to suggest a car-

of the ciliary body and iris, and to the cornea. The corneal branches pass to the annular plexus at the sclerocorneal junction from whence they are distributed to the corneal tissues. The long ciliary nerves supply the dilator muscle fibers of the iris. The short ciliary nerves supply the constrictor fibers.

APPENDAGES

The appendages of the eye include the eyelids, conjunctiva and lacrimal glands.

The Eyelids.—The eyelids are developed in the embryo through an invagination of the skin, which, leaving a slit-like aperture (the palpebral fissure) between its involuted margins, covers the inner surface of the lid to form the *palpebral conjunctiva*, and is reflected over the globe of the eye as the *ocular conjunctiva* and *anterior corneal epithelium*.

The lids, therefore, may be said to consist of two membranous portions, the cutaneous (outer or anterior) and the conjunctival (inner or posterior). Between these two portions the orbicularis palpebrarum forms a septum of striated muscle fibers.

Cutaneous Portion.—The cutaneous portion of the eyelid differs from other portions of the skin only in that its subcutaneous tissue contains no fat. The derma is loosely connected with the muscle by a wide-meshed areolar tissue. Fine hairs are distributed over the cutaneous surface, their follicles extending well down through the derma. Small sebaceous glands open into the hair follicles and occasional sudoriparous glands pour their secretion upon the epidermal surface.

At the margin of the lid its cutaneous portion is reflected inward, and at its inner angle becomes directly continuous with the palpebral conjunctiva. The free margin of the lid presents, therefore, an *outer angle*, an *inner angle*, and an *intermediate surface.*

Two or three rows of large stiff hairs, the eyelashes or *cilia*, project from the outer angle, and large sebaceous glands open into their follicles. Other smaller sebaceous glands open directly upon the free surface. These sebaceous glands are sometimes called the glands of Zeiss.

The intermediate surface of the margin of the lid retains the character of the skin, though no hairs are found in this portion. Peculiar sweat glands, the *glands of Moll*, occur in the derma of this part.

At the inner angle of the lid the epidermis abruptly changes its character to that of the conjunctiva, the derma of the cutaneous surface being continuous with the submucous connective tissue of this membrane. At the inner angle, also, are the openings of the peculiar large sebaceous glands, the *tarsal glands (of Meibom)*, their orifices forming a continuous punctate row of pores barely visible to the naked eye.

TARSAL GLANDS.—The tarsal (meibomian) glands are long compound saccular glands, about thirty in the upper, and about twenty in the lower lid, whose secreting saccules open into a common, axially placed duct which extends the whole length of the gland. Each saccule is filled with cells in various stages of

the epithelium become at first spheroidal and then, as the cornea is approached, they are progressively flattened, so that, just outside of the corneal margin, the conjunctival epithelium conforms to the stratified squamous type which forms the anterior epithelium of the cornea.

Blood Supply.—The blood supply of the eyelids is derived from the internal palpebral artery which furnishes a branch to each lid; these two branches anasto-

mose at the external angle with the lacrimal branch of the ophthalmic, through the external palpebral artery These transverse *arterial vessels (primary tarsal arches)* lie near the free margin of the lids between the tarsus and the obicularis palpebrarum muscle. Each tarsal arch sends *pre-tarsal* twigs forward to supply the muscle and integument, and *post-tarsal* twigs backward to supply the tarsal fascia, the tarsal glands and the conjunctiva. At the basal end of the tarsus, just back of the levator palpebrae muscle, a second arch (*secondary tarsal arch*) may be present, more commonly in the upper lid. This second arch represents a larger branch of the palpebral artery, and it anastomoses freely with the primary arch.
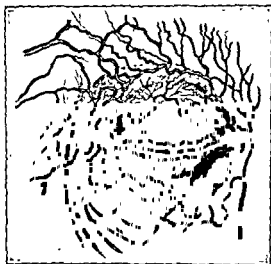
FIG. 582.—ARTERIAL SUPPLY OF THE EYELID

(Fox.)

The *veins* follow an essentially similar course. The *lymphatics* likewise include a *pre-* and *post-tarsal* set, which unite to form larger tarsal tributaries which drain along the facial vein toward the submaxillary lymph nodes.

Burch[10] has investigated the superficial lymph supply of the eyelid. The major vessels course parallel to the lid margin (Fig 583). There are at least four main vessels, two coursing medially and generally two laterally. There may be three or four vessels in the lateral portion of the upper lid. Both groups of parallel vessels unite medially and laterally to form common trunks.

Nerve Supply.—The nerve supply includes sensory, motor and autonomic fibers. The main trunks lie between the tarsus and the orbicularis palpebrarum muscle. The autonomic fibers supply the blood vessels, the smooth muscle of Muller, and the glands Motor fibers contributed by the facial nerve, supply the annular sheet of striped muscle.

The oculomotor nerve contributes motor fibers to the levator palpebrae muscle. The sensory fibers, which are derived from the trigeminal nerve, end in naked fibrils among the cells of the external integument and the internal conjunctiva, and in the subcutaneous connective tissue and the tarsus. Numerous sensory fibrils end also in special end-bulbs, especially along the inner margin of the lids; similar endings occur in the palpebral and bulbar conjunctiva.

[10] Burch, 1938.

tilaginous structure. It is inserted between the conjunctiva and the orbicularis muscle. It is thickest toward the free margin of the lid, but becomes progressively thinner in the opposite direction, until, as a mere fibrous membrane, the *palpebral fascia*, it is continued to the margin of the orbit.

Conjunctival Portion.—The conjunctival portion of the lids, the *palpebral conjunctiva*, consists of a peculiar stratified epithelium and a thin connective tissue corium. Its epithelium comprises four or five layers of cells, the deeper of which are small and spheroidal, and the superficial elongated or conical, their blunt ends forming the free surface of the conjunctiva, their pointed extremities buried between the cells of the deeper layers. The bases of these elongated cells become somewhat expanded and broader from the increased tension of the conjunctiva when the lids are closed; they retract and become narrower when the lids are separated and the conjunctiva relaxed.

The cells of the superficial layer are often so distinctly elongated as to possess a columnar form. They may, however, be spheroidal or even somewhat flattened, in which case they closely resemble the ordinary type of stratified squamous epithelium. The epithelial layer rests almost directly upon the connective tissue corium, the basement membrane being imperfectly developed.

The corium of the conjunctiva is thin. With the aid of a thin layer of submucous areolar tissue it unites the epithelium to the tarsus and to the fibers of the orbicularis muscle; near the margin of the lid its submucous tissue incloses the meibomian glands. Opposite the plane at which the blind ends of the meibomian glands are embedded in the free margin of the tarsus, the conjunctival surface is thrown into eight to twelve horizontal folds, beneath which, in the connective tissue, are a few minute tubulo-alveolar glands, the *posterior tarsal glands* (glands of Waldeyer, glands of Henle). Their ducts open upon the free surface of the conjunctiva near the fornix conjunctivae.

At the attached base of the lid a narrow band of smooth muscle extends from the levator palpebrae and inferior oblique muscles into the body of the lid. These fibers have been described by H. Müller (1858) as the superior and inferior *palpebral muscle* of the upper and lower lid, respectively, and have come to be known as the muscle of Müller.

The fold by which the palpebral conjunctiva is reflected upon the globe of the eye to become continuous with the ocular portion of the membrane is known as the *fornix conjunctivae*. The extremely loose attachment of the conjunctiva of the fornix to the underlying connective tissue and intra-orbital fat permits the great freedom of motion which is characteristic of the ocular globe. The small *accessory lacrimal glands* (glands of Krause) open into the margin of the fornix conjunctivae. The superior fornix contains from eight to twenty, the inferior from two to five. In this region, also, occasional goblet cells occur in the superficial layers of the epithelium.

The ocular conjunctiva is likewise very loosely attached to the sclera. The scleral portion of the conjunctiva is nearly identical in structure with the palpebral portion already described. Near the margin of the cornea the superficial cells of

portion and the inferior lobe or *palpebral portion*, and are united by thin fibrous fasciae which contain the larger ducts.

Each lobule of the gland contains many serous-secreting acini and numerous small intralobular ducts. The secreting acini are lined with tall columnar cells, resting upon a thin basement membrane, which is supplied with basket cells and is invested with a delicate fibrous lamina propria. The appearance of the

FIG 584—SECTION THROUGH A LOBULE OF THE LACRIMAL GLAND OF MAN.

a, small duct branching within the lobule; *b*, intercalary ducts; *c*, connective tissue; *f*, fat cells. *d*, transection of an interlobular duct. Hematoxylin and eosin. ×112 (Kölliker)

secreting epithelium differs somewhat according to its state of activity. After a period of rest, and in the ordinary condition of relative inactivity, the epithelium becomes distended with secretion and is either clear in appearance or at most is only very finely granular.

The nuclei are crowded to the base of the swollen cells, and the lumen of the acinus is very small After a period of excessive activity the secreting cells become shrunken and more distinctly granular, and the lumen of the acinus appears much dilated

The secreting acini empty into narrow *intercalary ducts* which lie within the lobule, have a considerable lumen, and are lined with tall columnar cells resting upon a second incomplete layer of small, somewhat flattened basket cells.

These *intralobular ducts* unite at the margin of the lobule to form the larger *interlobular ducts*, which are contained in the interlobular connective tissue. Here the duct is lined with low columnar or even somewhat flattened cells, at first

The Lacrimal Lake.—In the ⊃-shaped area of the internal canthus, the *lacus lacrimalis*, lies a roughened irregular reddish mass of delicate modified skin, the caruncle (*caruncula lacrimalis*). It is embedded in fat and contains a number of very delicate hairs, large sebaceous glands and a few sweat glands. Where the borders of the lake pass into the palpebral margins there appears a slightly raised *papilla lacrimalis*, each of which contains an apical opening, the *puncta lacrimalia*, leading into the two *canaliculi lacrimales*, which conduct the excess of lacrimal

Fig. 583—A Composite Drawing of the Superficial Lymphatics of the Eyelids as Observed in Twenty-five Normal Living Subjects.

The arrows indicate the sites of dye injection. (Burch)

secretion or tears into the *nasolacrimal* duct. To the outer side of the lacrimal lake there appears a vertical crescentic fold of delicate skin, the *plica semilunaris*, which is the homologue of a functional third eyelid (nictitating membrane) of birds and reptiles.

The Lacrimal Gland.—The lacrimal glands are two flattened, lobulated, glandular masses situated at the upper and outer angle of the orbit, one in relation with each eye. They secrete a clear watery fluid, the tears. These glands are somewhat molded to conform to the shape of the orbit and the globe of the eye, between which they are inserted.

Each lacrimal gland is a secreting gland of the compound tubular type (Fig. 270), and consists of eight to twelve small lobules which open into the fornix conjunctivae by about as many minute ducts. The lobules are aggregated into two fairly distinct lobes, separated by a denser fascia, the superior lobe or *orbital*

portion and the inferior lobe or *palpebral portion,* and are united by thin fibrous fasciae which contain the larger ducts.

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CHAPTER XIX

THE EAR

This organ may be subdivided for description into the external, the middle, and the internal ear. The first two portions serve for the collection and transmission of sound waves, the last for the transformation of the sound waves into nerve stimuli which are then transmitted through the path of the acoustic nerve to the cerebrum.

EXTERNAL EAR

The external ear includes an auricular or free portion and an external acoustic (auditory) meatus

Auricle.—The auricle, or *pinna*, contains a thin cartilaginous plate of peculiar form which is covered on both sides by the skin. The cartilage is of the elastic variety, but differs from the similar cartilages of other parts in the abundance of its large cartilage cells; in occasional areas the elastic reticulum is deficient. This reticulum is closely connected with the fibrous perichondrium, beneath which it forms a complete layer. The extrinsic muscles of the ear are inserted into the perichondrium and the fibrous tissue by which it is surrounded.

The skin of the external ear does not differ essentially from that of other parts. It is supplied with fine hairs and with many large sebaceous glands; sweat glands also occur on the outer surface. The derma is united to the underlying cartilage by connective tissue; on the concave surface this union is very firm and permits but little motion. The subcutaneous tissue, except in the lobule, contains but little fat. The lobule does not contain cartilage.

External Acoustic Meatus.—The external acoustic meatus (or auditory canal) is divisible into an outer cartilaginous and an inner bony portion; the walls of the two portions, except for this difference, are quite similar in structure. The cartilaginous division constitutes the external one-third, about 8 millimeters in length. The cartilage is continuous with that of the auricle, and is of the cellular elastic variety. The skin of this portion contains large stiff hairs and both sebaceous and ceruminous glands. The former, as in the auricle, open either upon the free surface of the skin or into the adjacent portion of the hair follicles.

Ceruminous Glands.—The ceruminous glands resemble in structure the sweat glands of other portions of the body. They are coiled tubular glands which open upon the surface of the skin by means of a narrow duct. The coils of their secreting portion are lined with columnar cells with spheroidal, basally situated nuclei and a clear cytoplasm containing many small brownish granules of pigment

disposed in a single, but later in a double layer. As the duct approaches the conjunctival surface the number of cells layers increases until their lining epithelium finally comes to resemble the stratified epithelium of the conjunctiva with which it is continuous.

Extracts of the lacrimal glands have been shown to cause a sharp contraction of the smooth muscle of the blood vessels and the uterus, and to stimulate heart

FIG. 585—PORTIONS OF TWO ADJACENT LOBULES OF THE LACRIMAL GLAND OF THE RABBIT, SHOWING TWO STAGES IN SECRETORY ACTIVITY OF THE TUBULES.

In the upper lobule the cells are filled with minute, in the lower lobule with large, secretion spherules ×100.

action. These properties suggest the probability of an internal secretion in these glands.[11]

Minute collections of diffuse lymphoid tissue and even small lymph nodules are occasionally found just beneath the epithelium of the conjunctiva in the neighborhood of the lacrimal glands of the fornix; occasionally the lymphoid tissue is quite abundant.

In animals possessing a membrana nictitans (third lid) a small, mucus-secreting gland occurs at the inner angle of the orbit; this is known as the *gland of Harder*. It is well developed also in some mammals, *e.g.*, rabbit, but in man and other primates it is usually absent, though in an extremely vestigial condition it may occasionally be found within the basal portion of the plica semilunaris.

11 Michail and Vancea, 1931.

meatus and separates it from the cavity of the middle ear, the skin is reduced to an extremely thin cutaneous coat, devoid of hairs, glands and papillae.

MIDDLE EAR

The middle ear or *tympanum* (ear drum) is an irregular cavity, broad above and behind, narrow below and in front, which lies just within the external acoustic meatus. Its outer wall is largely formed by the tympanic or drum membrane, its inner by the osseous wall of the internal ear.

FIG. 587.—FROM THE EXTERNAL ACOUSTIC MEATUS OF MAN.

a, sebaceous gland; *b*, ceruminous gland; *c*, cartilage. ×15. (Sobotta.)

The contour of the tympanum is very irregular, its cavity being encroached upon by numerous bony elevations which are most pronounced on its internal wall. Externally the tympanic membrane is attached to a bony and fibrocartilaginous ring, the *annulus tympanicus*, which projects somewhat into the tympanic cavity. In front, the orifice of the auditory (eustachian) tube is marked by a slight cartilaginous projection near the floor of the cavity.

Above and behind, the tympanic cavity is prolonged into a deep recess, the *epitympanic cavity*, in the upper part of whose posterior wall are the orifices of the mastoid cells. The upper portion of the cavity contains the rounded heads of the malleus and incus, the two largest of the auditory ossicles. The internal wall of the tympanum presents anteriorly a bulging prominence which is known as the *promontory*, and which indicates the position of the first or broadest turn

and a few fatty particles. The cytoplasm is often diffusely colored by the brownish pigment. Between the lining cells and the basement membrane appear slender fusiform elements resembling similarly placed elements in the sweat glands, and likewise interpreted as smooth muscle cells (myo-epithelium). The secretion of these glands, the cerumen, in addition to the pigmented and fatty secretion of the
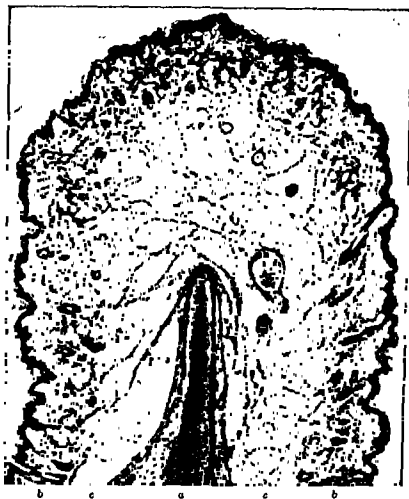
FIG. 586—TRANSECTION OF THE LOBULE OF THE EXTERNAL EAR OF AN INFANT.
a, cartilage; *b*, skin, *c*, adipose connective tissue. Hematein and eosin. Photo. ×20.

glands, contains sebum, desquamated epithelial cells and occasional fine hairs, together with foreign particles of a varied sort. The ceruminous glands may be classified as of the apocrine variety.

In the bony portion of the meatus the corium or derma is firmly adherent to the periosteum of the bone, and all the layers of the skin are much reduced in thickness. The scanty hairs are fine, and, with the glands, are continued inward to the tympanic membrane only in the superior portion of the wall of the canal. Papillae are present as far as the margin of the tympanic membrane. Upon the surface of this membrane, which closes the inner end of the external acoustic

internal, and posterior walls also possess a partial clothing of low ciliated cells (Kessel). Occasional gland-like folds of the mucosa occur near the orifice of the auditory tube, though the true glandular character of these folds is questionable.

Mastoid Cells.—The mastoid cells (*cellulae mastoideae seu pneumaticae*) are numerous small spaces situated within the mastoid process of the temporal bone.

FIG. 589.—SECTION THROUGH THE MARGIN OF THE TYMPANIC MEMBRANE OF A CHILD.

a, fibrocartilaginous ring; *b*, bone; *c*, derma of the external auditory canal; *d*, tympanic mucosa; *e*, *c′*, epidermis, *f*, radial fibers, and *f′*, circular fibers of the tympanic membrane; *g*, mucosa of the membrane; *h*, epithelium of the tympanum; *i*, blood vessels ×55 (Kölliker.)

They are lined by a continuation of the tympanic mucosa, which is everywhere clothed with flattened epithelium. The corium is closely attached to the periosteum of the bony wall, the periosteum also serving as a vascular layer of the mucosa in the mastoid cells, as well as in the general tympanic cavity.

Tympanic Membrane.—The tympanic membrane is a thin delicate partition which is formed by a reflection of the cutaneous layer of the external acoustic

of the spiral canal of the cochlea. Beneath this prominence is a recess leading to a bony "window," the *fenestra cochleæ* (or fenestra rotunda), which, in life, is closed by a delicate membrane, the secondary tympanic membrane. Behind the promontory and at a slightly higher level a deep recess, the *pelvis ovalis*, leads inward to the *fenestra vestibuli* (or *fenestra ovalis*), which is closed by the base
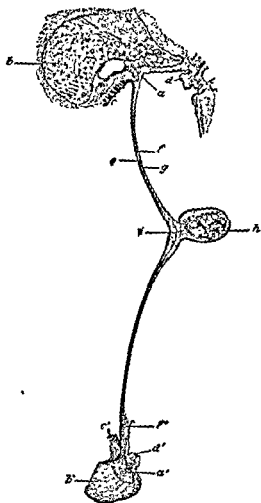
Fig. 588.—Transection of the Tympanic Membrane of a Child

a, *a′*, fibrocartilaginous ring; *b*, *b′*, bone; *c*, *c′*, skin of the external acoustic meatus; *d*, *d′*, tympanic mucosa; *e*, cutaneous layer of the tympanic membrane; *f*, fibrous layer, obliquely cut at *f′*; *g*, layer derived from the tympanic mucosa; *h*, handle of the malleus; *i*, blood vessels. ×11. (Kölliker.)

of the stapes. The body of this ossicle is contained entirely within the pelvic recess, and near its mouth the stapes articulates with the orbicular extremity of the long process of the incus. The superior portion of this deep recess is encroached upon by the projecting wall of the *aqueduct of Fallopius* which transmits the *facial nerve*, and posteriorly, near the point where it merges with the general tympanic cavity, a low, conical, bony projection known as the *pyramid* transmits the *stapedius muscle*. The canal of the *tensor tympani muscle* contained within a still more prominent, conical, bony projection, the *processus cochleariformis*, is found near the antero-internal angle of the tympanic cavity just above and parallel to the auditory tube. The narrowest portion of the tympanum is near its center, and is included between the promontory on the inner and the tympanic membrane on the other side. Extending from this narrowed central portion upward, backward, and inward, are expanded recesses which are partially occupied by the three auditory ossicles. The remaining portions of the tympanum are filled with air which gains access to the cavity through the auditory tube.

Tympanic Mucosa.—The tympanic mucosa consists of a thin but dense lamina propria which is firmly attached to the underlying periosteum and softer parts by loose connective tissue. It is clothed with a layer of flattened entodermal epithelium, which, in the vicinity of the origin of the auditory tube, is of low columnar form and is provided with cilia In most other portions of the tympanum it is squamous in character and of the tessellated type, closely resembling endothelium. The floor of the tympanum and the lower portions of its anterior,

internal, and posterior walls also possess a partial clothing of low ciliated cells (Kessel). Occasional gland-like folds of the mucosa occur near the orifice of the auditory tube, though the true glandular character of these folds is questionable.

Mastoid Cells.—The mastoid cells (*cellulae mastoideae seu pneumaticae*) are numerous small spaces situated within the mastoid process of the temporal bone.

FIG. 589—SECTION THROUGH THE MARGIN OF THE TYMPANIC MEMBRANE OF A CHILD.

a, fibrocartilaginous ring; *b*, bone; *c*, derma of the external auditory canal; *d*, tympanic mucosa; *e*, *e'*, epidermis; *f*, radial fibers, and *f'*, circular fibers of the tympanic membrane; *g*, mucosa of the membrane; *h*, epithelium of the tympanum; *i*, blood vessels. ×55 (Kölliker.)

They are lined by a continuation of the tympanic mucosa, which is everywhere clothed with flattened epithelium. The corium is closely attached to the periosteum of the bony wall, the periosteum also serving as a vascular layer of the mucosa in the mastoid cells, as well as in the general tympanic cavity.

Tympanic Membrane.—The tympanic membrane is a thin delicate partition which is formed by a reflection of the cutaneous layer of the external acoustic

meatus on the one hand, the tympanic mucosa on the other, and between these two membranes a layer of dense fibrous tissue whose tendinous bands are disposed in radial and circular directions. The margin of the tympanic membrane is inserted into a fibrocartilaginous ring which rests upon a bony elevation, the *annulus tympanicus.*

The slender manubrium or handle of the malleus projects from the superior margin of the ring and is inserted between the folds of the tympanic membrane, extending downward to about the center of the membrane, at which point is the deepest part of its concavity, its *umbo.* The bony handle of the malleus, lying

FIG. 590—THE AUDITORY OSSICLES.

I, ossicular chain of the left ear; *1,* malleus; *2,* incus; *3,* stapes. *II,* ossicular chain of the right ear; *1,* malleus; *2,* processus gracilis; *3,* manubrium; *4,* long process of the incus; *5,* short process of the incus; *6,* stapes. (Rudinger.)

between the cutaneous and mucous layers of the tympanic membrane, is covered by a thin cartilaginous layer, and receives the insertions of the tendinous fibers. These fibers are divisible *into an outer radial layer* which extends from the fibrocartilaginous ring at the periphery inward to the manubrium mallei, and an inner circular layer whose thickest portions are found close to the manubrium and near the periphery of the membrane. Between these points the circular layer of fibers is partially or entirely deficient. Just within the fibrocartilaginous ring at the periphery of the membrane the circular layer of fibers abruptly ends.

The cutaneous layer of the tympanic membrane forms a thin coat, its epidermis consisting of a germinal layer one or two cells deep, which is covered by several flattened non-nucleated cells of the horny portion. The derma or corium is very thin, contains no papillae, and is intimately adherent to the fibrous layers of the membrane; it contains neither glands nor hairs.

The mucous layer of the tympanic membrane is even thinner than the cutaneous. It consists of a flattened entodermal epithelium which rests almost directly upon the layer of circular fibers. A few connective tissue fibers pass irregularly

from the mucous layer through the fibrous, to the cutaneous layer. In this way the several layers of the tympanic membrane are firmly united into a compact membrane.

In the upper quadrant of the tympanic membrane, above the attachment of the malleus, the fibrous layers are wanting; the mucous and cutaneous layers are therefore in contact, and the membrane presents a flaccid appearance in comparison with the tense condition of its other parts. This portion is known as the *membrana flaccida* or *Shrapnell's membrane*.

Auditory Ossicles.—These are three in number, the *malleus*, the *incus*, and the *stapes*. They form a continuous bony chain, extending from the insertion of the manubrium mallei in the tympanic membrane to the fenestra vestibuli, with whose margin the foot of the stapes articulates. The ossicles consist of compact bony tissue containing loosely packed haversian systems; they are united with each other by firm fibrocartilaginous articulations. With the exception of the stapes, none of the ossicles contains a marrow cavity.

FIG. 591.—THE CAVITY OF THE TYMPANUM, VIEWED FROM ABOVE

i, the body of the incus; *l*, ligamentous fold of the mucosa; *l a.m.*, anterior ligament of the malleus; *l c.m.*, external ligament of the malleus; *l.i.*, posterior ligament of the incus; *M*, mastoid cell; *m*, head of the malleus; *m m.*, mucous membrane; *n*, chorda tympani nerve; *pr.o.*, orbicular process of the incus articulating with the stapes in the depth of the cavity; *R*, beneath this space is the flaccid portion of the tympanic membrane; *s.l m.*, cut end of the superior ligament of the malleus; *sp*, spina tympanica anterior; *st*, *st'*, tendon of the tensor tympani muscle. ×4 (Schafer.)

The manubrium of the malleus is firmly fixed in the tympanic membrane, as already described, the head of the bone articulating with the head of the incus in the epitympanic recess. The long process of the incus, circular in transection, extends downward along the tympanic wall in a course nearly parallel to that of the manubrium mallei, being, in a portion of its course, contained within a recess in the osseous wall of the tympanum. Finally, at the level of the stapes it makes a sharp bend, almost at right angles with its former course, to articulate, by means of a rounded end or *orbicular process*, with the head of the stapes. This latter bone is deeply placed within the recess of the pelvis ovalis, and continues the bony chain to the fenestra vestibuli, where the foot plate of the stapes is in relation, by its inner surface, with the vestibular perilymphatic space of the internal ear.

The course of the chain of ossicles is such that they form a lever. Since the long process of the incus is shorter than the manubrium mallei, the vibrations of the tympanic membrane in response to sound waves are transmitted to the internal ear diminished in amplitude but exaggerated in intensity. The combined activity of the tympanic membrane and the auditory ossicles is said to reduce the

Vascular Supply.—*Blood Vessels.*—The mucosa of the middle ear is richly supplied with blood vessels, the larger of which lie in the deeper part of the membrane and supply capillary vessels to the lamina propria. The blood vessels of the auditory tube are especially numerous.

In the tympanic membrane the arteries and veins form an annular plexus at the margin. A group of similar vessels surrounds the manubrium mallei, lying in the deeper layers of the cutaneous portion of the membrane.

The mucosa of the tympanum is peculiar in the relative deficiency of capillary vessels (Prussak, 1869); the veins are numerous. The veins of the auditory tube empty into the internal jugular. They also communicate with the cavernous sinus by a trunk of considerable size.[1]

Lymphatics.—The lymphatics of the middle ear form plexuses in the connective tissue of the mucosa and in a general way follow the course of the smaller veins. They lead in part to the lymph nodes behind the ear, and in part to the parotid group (Kölliker). They also communicate with the perilymphatic spaces of the internal ear.

INTERNAL EAR

The internal ear includes a series of membranous structures together with the terminal fibers of the acoustic nerve. These are contained within a series of connected cavities hollowed out of the petrous portion of the temporal bone, and in relation with the mesial wall of the tympanum. The central portion of this bony cavity, an ovoid space, is known as the *vestibule*. Its outer wall presents the orifice of the fenestra vestibuli which leads to the tympanum, but during life is closed by the base of the stapes. Opening from the vestibule, at one end, are the bony cavities occupied by the three semicircular canals which, in a general way, project from the posterodorsal aspect of the vestibule. At the other end the bony cochlea containing its series of spiral canals projects anteriorly from the vestibule. Collectively these spaces, with several diverticula, form the *bony labyrinth*. Within them in life are contained a number of membranous sacs whose general form corresponds more or less closely to that of the bony cavity. These sacs collectively form the *membranous labyrinth.*

The vestibule contains two of these membranous sacs, the *sacculus* and the *utriculus*, which are connected by means of the slender *utriculosaccular canal*. From this canal a much prolonged diverticulum enters the *aqueductus vestibuli* to penetrate to the posterior surface of the petrous bone where it comes into relation with the cerebral meninges. This diverticulum is known as the *ductus endolymphaticus*. Its dilated terminal portion constitutes the *endolymphatic sac*, which lies upon the dura and probably opens into the subdural space. According to Guild[2] the escape of endolymph is not through actual openings in the wall, but by direct passage through the layers of the wall, being thus comparable to the

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[1] Dench, 1895.
[2] Guild, 1927.

flow of cerebrospinal fluid through the arachnoid villi. The utricle and saccule, as also all other portions of the membranous labyrinth, contain a watery fluid, the *endolymph*. They do not entirely fill the bony cavity of the labyrinth in which they lie, the intervening space being occupied by a retiform connective tissue with broad interstices which are permeated by an aqueous fluid, the *perilymph*.

Saccule.—The saccule is a rounded membranous cavity which is connected, on the one hand, by means of the slender *canalis reuniens,* with the cochlear duct or scala media, and on the other hand with the ductus endolymphaticus and
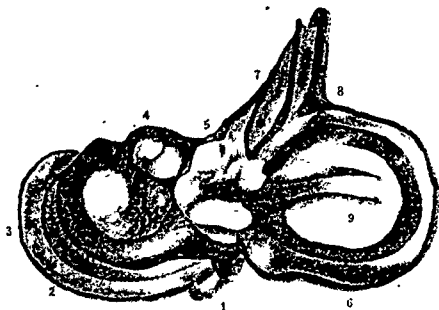
FIG. 593.—THE BONY LABYRINTH.

1, round window; *2,* osseous lamina spiralis; *3,* osseous cochlear canal; *4,* floor of internal acoustic meatus; *5,* vestibule, *6, 7, 8, 9,* semicircular canals. The figures are placed at that portion of the margin which is nearest the structure indicated. (Rudinger.)

utricle, as already stated. Its wall consists of an ectodermal epithelium, a membrana propria and a fibrous lamina. The epithelium consists of flattened squamous cells; it completely lines the cavity. The epithelial surface is somewhat irregular from the papillary elevations of the fibrous coat. On the antero-inferior surface of the saccule the epithelium is peculiarly altered so as to form a layer of columnar cells, many of which are provided with stiff cilia. This *neuro-epithelium* is distributed over an oval area (3 by 2 millimeters in extent) beneath which the fibrous coat is much thickened by the entrance of many fibers derived from the vestibular portion of the acoustic nerve. This elevation with its neuro-epithelial covering is known as the *macula acustica sacculi.*

The neuro-epithelium contains two varieties of cells, the *sustentacular* and the *hair* cells. The former, *fiber cells* of Retzius, form a layer, two or three cells deep, which rests upon the basement membrane. The broad basal portion of the

fiber cell contains a spheroidal nucleus. Beyond the nucleated portion the cyto-
plasm of the sustentacular fiber cell is continued inward between the bodies of
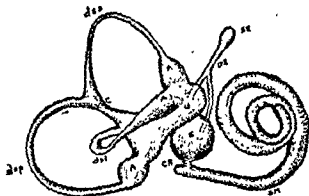
FIG. 594.—MEMBRANOUS LABYRINTH IN LATERAL VIEW.

A, ampullae; *U*, utricle; *S*, saccule; *SM*, scala media or cochlear duct; *CR*, canalis reuniens;
C, crus, or common canal; *SE*, saccus endolymphaticus; *DE*, ductus endolymphaticus; *dss, dsp,
dsl*, superior, posterior and lateral (external) semicircular ducts. The utricle and saccule are
connected by the utriculosaccular duct. The cochlear duct terminates in the ceca vestibulare and
cupulare. (*Gray*)

the hair cells to the surface of the epithelial layer, this portion of the cell being
relatively slender.

The hair cells occupy the superficial part of the epithelial layer by their broad
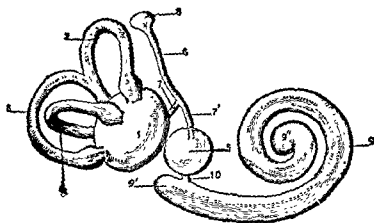
FIG. 595.—RIGHT MEMBRANOUS LABYRINTH.

1, utricle; *2*, superior semicircular canal; *3*, posterior semicircular canal; *4*, external semi-
circular canal; *5*, saccule; *6*, endolymphatic duct; *7* and *7'*, canals connecting utricle and saccule
respectively with the endolymphatic duct; *8*, endolymphatic sac; *9*, cochlear duct; *9'*, its vestibular
culdesac (cecum vestibulare); *9"*, its terminal culdesac (cecum cupulare); *10*, canalis reuniens
(Testut)

nucleated portions, which carry upon their free extremity a single tuft of long
stiff cilia, having the appearance of a delicate hair-like process which projects
into the endolymphatic cavity. That portion of the endolymph which immediately

overlies the macula, and into which the hair-like processes project, though not essentially different in microscopic appearance in fresh tissues, appears to possess a somewhat gelatinous consistence. In this jelly are suspended various forms of minute crystals of calcium carbonate which are known as otoconia or "otoliths." The free surface of the neuro-epithelium is also provided with a reticulated cuticular membrane which presumably is formed by the amalgamation of the
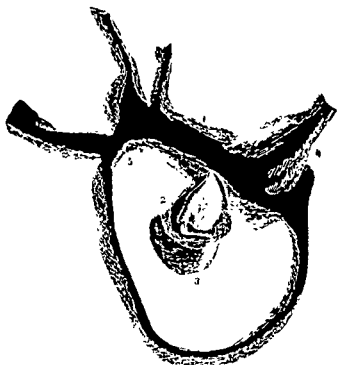
FIG. 596—THE ISOLATED MEMBRANOUS LABYRINTH.

1, utricle; *2*, saccule (opened); *3*, location of the macula acustica sacculi; *4*, ampulla of a semicircular canal; *5*, canalis communis. Low magnification. (Rüdinger.)

free ends of the sustentacular cells. Through the openings in this reticular membrane the ciliary tufts of the hair cells project.

The central ends of the hair cells, beneath the nucleated enlargement which is found near the middle of the epithelial layer, are prolonged outward between the nucleated portions of the sustentacular cells and frequently terminate in small knobbed extremities. This portion of the cells is in intimate relation with the terminal fibrils of the vestibular portion of the acoustic nerve, which, coming from a nerve plexus in the fibrous wall of the saccule, forms an intra-epithelial plexus of delicate varicose fibrils. Frequently the epithelial coat contains coarse granules of a brownish pigment which, at times, also produces a diffuse coloration of the cells.

The lining epithelium of the saccule rests upon a thin homogeneous basement membrane and is further supported by a delicate fibrous coat or lamina propria. The connective tissue of this coat forms interlacing bundles, most of which are distributed in a circular manner about the wall of the ovoid sacculus. At the

macula this coat is much thickened by the entrance of the fibers from the vestibular nerve. It also contains the minute blood vessels which supply the organ.

As is the case with the other divisions of the membranous labyrinth, the

FIG. 597.—TRANSECTION OF THE MARGIN OF THE MACULA ACUSTICA SACCULI OF A GUINEA-PIG.

a, otolithic membrane; *b*, hairs; *c*, cuticular membrane; *d*, hair cells; *e*, sustentacular cells; *f*, epithelium of the saccule; *g*, tunica propria; *h*, nerve fibers; *i*, bone ×325. (Kölliker.)

fibrous wall of the saccule is in contact on one aspect of its surface with the periosteum which lines the osseous labyrinth; elsewhere it is separated from the periosteum by the perilymphatic cavity.

Utricle.—The utricle is somewhat larger than the saccule. It lies behind and somewhat above the saccule, is of a very irregular oblong form, and receives the

FIG 598 —NERVE ENDINGS IN THE MACULA ACUSTICA OF A GUINEA-PIG.

a, epithelium; *b*, tunica propria; *c*, three terminal nerve fibers. Golgi stain × about 200 (Retzius.)

insertions of the semicircular canals. Its anterior portion is provided with a *macula* and the structure of its wall differs in no wise from that of the saccule.

A fold of areolar tissue covered with cuboidal epithelium, the "utriculo-endolymphatic valve" of Bast,[3] situated on the posterior wall of the utricle at its junction with the endolymphatic duct, projects into the utricle and guards the opening of the duct.[4] The valve serves presumably to prevent an outflow of endolymph from the utricle under conditions of sudden pressure changes (Bast).

Semicircular Ducts.—The semicircular ducts or canals are three in number, the posterior, superior, and lateral. The last is also horizontal in its position; the

[3] Bast, 1928.
[4] Wilson and Anson, 1929

first two are vertical, but are so placed as to form a right angle with one another. The posterior lies in the long axis of the petrous bone and its plane is therefore more nearly sagittal, while that of the superior canal is more nearly coronal. Each canal forms something more than half a circle, its two ends opening separately into the cavity of the vestibule, with the exception of the posterior and superior canals whose internal ends open by a common orifice, the *canalis communis*. The
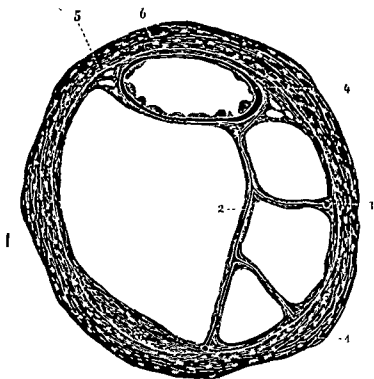
FIG. 599—TRANSECTION OF A HUMAN SEMICIRCULAR CANAL.

1, bone; *2*, retiform connective tissue membranes; *3*, at this point a band of connective tissue joins the periosteum; *4*, membranous semicircular canal; *5*, ligamentous attachment of the canal; *6*, at this point the membranous and osseous canals are in contact. Moderately magnified. (Rudinger.)

unjoined orifices of the posterior and superior ducts, as also the outer extremity of the lateral duct, present a marked dilatation at their termination in the vestibule. These dilatations are known as the *ampullae*. They lodge the neuro-epithelial patches, the cristae acusticae. The osseous and membranous ducts are of similar shape. The membranous duct is, of course, contained within the former.

The membranous semicircular canals open into the utricle. They do not entirely fill their bony canal, but, like the utricle and saccule, lie in contact with the periosteum at one surface only. This surface of contact is along the outer wall or periphery of the semicircle, while in the remaining portion of the circumference of the cylindrical bony duct, the membranous canal is loosely united to the periosteum of the osseous wall by a retiform connective tissue whose loose meshes are filled with perilymph and lined with mesenchymal epithelium.

The wall of the membranous duct is similar in structure to that of the saccule and utricle and consists of an ectodermal epithelium, a membrana propria, and a fibrous tunic. Each of the three ampullae presents a marked differentiation of the epithelial lining, which is there raised in the form of a prominent crescentic fold, inappropriately termed by the older anatomists the *crista acustica*, from its supposed connection with the auditory function. Like the maculae of the saccule and utricle, the cristae are supplied by the vestibular nerve and are concerned with the function of equilibration.

The utricle and saccule represent the original primordium of the ear—the otocyst—from which the ducts and cochlea arise as evaginations; they correspond most closely also to the "ear" of certain invertebrates, *e.g.*, crustacea, which is simply an equilibrating organ. They are believed to function as static organs of equilibration, giving information as to position at rest or during progressive movements. The semicircular ducts on the other hand are commonly conceived of as dynamic organs of equilibration and are thought to furnish information regarding the direction and extent of rotatory movements.

The cristae are clothed with tall columnar cells which, though somewhat taller, are otherwise similar in structure to those of the maculae, and are similarly divisible into sustentacular cells and hair cells. They are also covered by a gelatinous cuticular formation, containing otoliths, which is here known as the *cupula terminalis*. The vibratory stimulus is transmitted from the endolymph to the hair cells through the medium of the otolithic membranes.

FIG. 600.—AXIAL SECTION THROUGH THE COCHLEA OF A FETAL CALF.

a, internal acoustic meatus in which is the cut end of the cochlear nerve as it enters the modiolus. ×6. (Kölliker)

Cochlea.—The cochlea, like the vestibular portion of the internal ear, consists of a bony case which incloses a membranous organ.

Structure.—The bony cochlea possesses a peculiar flat pyramidal shape. The base of the pyramid is in contact with the anterior aspect of the vestibule; its apex or *cupola* is directed forward, outward, and slightly downward. The pyramid is hollow and contains in its axis a conical bony support, the *modiolus*, which tapers from a broad base to a pointed apex beneath the broader, blunt, and rounded cupola of the outer bony wall. The modiolus contains a broad canal which receives the cochlear division of the acoustic nerve as it enters from the internal meatus.

The outer surface of the modiolus supports a bony shelf, the *lamina spiralis ossea*, which winds in a spiral manner from its base to its apex, and ends in a hook-like process, the *hamulus*. This shelf only partially spans the interval between the modiolus and the outer wall of the cochlea. In life the remaining interval is completed by a firm fibrous membrane, the *basilar membrane* (*lamina spiralis membranacea*). Thus the cylindrical canal of the cochlea, which is wound spirally

around the modiolus making two and one-half turns from the base to the apex, is subdivided into two parallel longitudinal divisions, which are respectively known as the *scala vestibuli* and the *scala tympani*. They are so disposed that in a given turn of the canal the former is always nearer the apex, the latter nearer the base of the cochlea. According to Wiedersheim (1893) the human cochlea
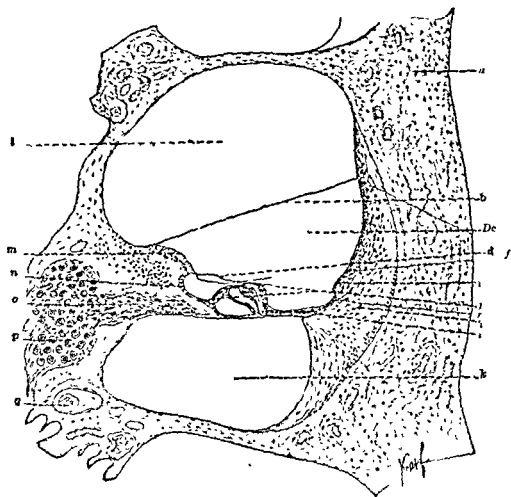
FIG. 601.—AXIAL SECTION THROUGH A TURN OF THE COCHLEA OF A GUINEA-PIG.

a, bone of the outer wall of the cochlea; *b*, membrane of Reissner; *d*, membrana tectoria; *Dc*, cochlear duct or scala media; *f*, stria vascularis; *g*, organ of Corti; *h*, spiral ligament; *i*, cells of Claudius; *k*, scala tympani; *l*, scala vestibuli; *m*, vestibular lip of the limbus spiralis, *n*, internal spiral sulcus; *o*, nerve fibers of the cochlear nerve, contained within one of the radiating canals within the osseous spiral lamina; *p*, nerve cells of the spiral ganglion; *q*, blood vessel; *r*, external spiral sulcus, upon which open Shambaugh's glands; *s*, prominentia spiralis, containing the vas prominens. ×90. (Bohm and von Davidoff.)

has nearly three turns, that of the pig four, the cat three, the rabbit two and one-half, the ox three and one-half, and cetacea one and one-half turns.

The osseous lamina spiralis presents a grooved margin or *sulcus*, from the basal or tympanic lip of which the lamina basilaris is continued to the opposing surface of the bony wall. The lamina spiralis ossea is hollowed out in a diploic manner for the transmission of the branches of the cochlear nerve, which are continuously given off all the way from the base to the apex of the osseous spiral

The wall of the membranous duct is similar in structure to that of the saccule and utricle and consists of an ectodermal epithelium, a membrana propria, and a fibrous tunic. Each of the three ampullae presents a marked differentiation of the epithelial lining, which is there raised in the form of a prominent crescentic fold, inappropriately termed by the older anatomists the *crista acustica*, from its supposed connection with the auditory function. Like the maculae of the saccule and utricle, the cristae are supplied by the vestibular nerve and are concerned with the function of equilibration.

The utricle and saccule represent the original primordium of the ear—the otocyst—from which the ducts and cochlea arise as evaginations; they correspond most closely also to the "ear" of certain invertebrates, *e.g.*, crustacea, which is simply an equilibrating organ. They are believed to function as static organs of equilibration, giving information as to position at rest or during progressive movements. The semicircular ducts on the other hand are commonly conceived of as dynamic organs of equilibration and are thought to furnish information regarding the direction and extent of rotatory movements.

The cristae are clothed with tall columnar cells which, though somewhat taller, are otherwise similar in structure to those of the maculae, and are similarly divisible into sustentacular cells and hair cells. They are also covered by a gelatinous cuticular formation, containing otoliths, which is here known as the *cupula terminalis*. The vibratory stimulus is transmitted from the endolymph to the hair cells through the medium of the otolithic membranes.

FIG 600—AXIAL SECTION THROUGH THE COCHLEA OF A FETAL CALF.

a, internal acoustic meatus in which is the cut end of the cochlear nerve as it enters the modiolus. ×6. (Kölliker)

Cochlea.—The cochlea, like the vestibular portion of the internal ear, consists of a bony case which incloses a membranous organ.

Structure.—The bony cochlea possesses a peculiar flat pyramidal shape. The base of the pyramid is in contact with the anterior aspect of the vestibule; its apex or *cupola* is directed forward, outward, and slightly downward. The pyramid is hollow and contains in its axis a conical bony support, the *modiolus*, which tapers from a broad base to a pointed apex beneath the broader, blunt, and rounded cupola of the outer bony wall. The modiolus contains a broad canal which receives the cochlear division of the acoustic nerve as it enters from the internal meatus.

The outer surface of the modiolus supports a bony shelf, the *lamina spiralis ossea*, which winds in a spiral manner from its base to its apex, and ends in a hook-like process, the *hamulus*. This shelf only partially spans the interval between the modiolus and the outer wall of the cochlea. In life the remaining interval is completed by a firm fibrous membrane, the *basilar membrane (lamina spiralis membranacea)*. Thus the cylindrical canal of the cochlea, which is wound spirally

window displacements are mechanically essential to audition. By plugging the round window with cotton or packing it with periosteum, Hughson and Crowe [5] found that such immobilization of this membrane in the cat actually increased the efficiency of the normal ear for sound conduction. They compare the action of the secondary tympanic membrane to a safety valve for the protection of the structures of the inner ear and for the absorption of a large percentage of the sound impulses that reach the cochlea. Pohlman [6] construes the evidence "to support the idea that the function of the round window is to act as a shock absorber on displacements in the cochlear liquid and is definitely opposed to an interpretation of the morphology of the internal ear in terms of mechanical reactions."

Having traced the general form and relations of the several portions of the cochlea, we are now in a position to study more carefully the finer structure of its more important parts.

Membranous Wall.—The membranous wall of the scala tympani and scala vestibuli is clothed with a mesenchymal epithelium of flattened endothelioid cells, which rest upon a double layer of fibrous tissue. Thus the lamina propria also serves as a periosteum for the inner surface of the bony wall of the cochlea, and conveys the blood and lymphatic vessels. The scalae are perilymphatic canals. They communicate with the subdural space through the aqueductus vestibuli and the aqueductus cochleae. The latter opens from the scala tympani near its beginning at the fenestra cochleae, and passes below the pyramid to the dura transmitting a small vein.

Vestibular Membrane.—The vestibular membrane (of Reissner) is an extremely delicate structure which consists of a thin central substantia propria, covered on either surface by epithelium, that on the one surface being continuous with the mesenchymal epithelium of the scala vestibuli, that on the other with the ectodermal epithelium of the scala media. It is nonvascular in the adult.

The outer wall of the scala media is lined by a continuation of the epithelium in that portion which adjoins the membrane of Reissner, and this rests upon a fibrous membrane similar to that which forms the walls of the other scalae. Toward the attachment of the membrana basilaris, however, the tissue of the outer fibrous wall of the scala media is much thickened, and forms a dense ligamentous structure, triangular in shape as seen in a longitudinal section of the cochlea This ligament receives the insertion of the membrana basilaris at its apex, and being, like the basilar membrane, continued from the base to the apex of the cochlea, is known as the *spiral ligament*. Its dense fibrous bands radiate from the attachment of the basilar membrane to all portions of the ligament, and are firmly attached to the bony wall of the cochlea, with whose periosteum the deeper fibers of the spiral ligament are blended.

The surface of the spiral ligament, which forms the outer wall of the scala media, slopes gradually away from the attachment of the basilar membrane; that

[5] Hughson and Crowe, 1932.
[6] Pohlman, 1932.

lamina, and which pass outward through the *foramina nervosa* upon the basilar membrane to be distributed to the epithelium of the *spiral organ* (*of Corti*). This organ is a peculiar spiral group of neuro-epithelial cells which extends the whole length of the basilar membrane from the base to the cupola of the cochlea.

The upper margin of the osseous spiral lamina is much thickened by the fibrous and epithelial tissues by which it is invested, so that a membranous sulcus of considerable depth is formed, the *sulcus spiralis internus*. The vestibular lip of this sulcus is further thickened by a marked elevation of fibrous tissue covered by columnar cells, from the outer margin of which a delicate membrane, the *membrana tectoria*, extends outward and overhangs the epithelium of Corti's organ. From the inner margin of the elevation of fibrous tissue, the *limbus spiralis*, a delicate membrane, the *vestibular membrane* (*of Reissner*), passes obliquely outward to the bony wall of the cochlea. In transections this membrane appears to cut off a corner of the scala vestibuli, thus marking off a triangular space whose base is formed by the outer wall of the cochlea, its sides by the membrane of Reissner and the basilar membrane upon which rests the organ of Corti; its blunt apex is found at the sulcus spiralis internus. Since these membranes extend the entire length of the bony spiral canal of the cochlea, the space which is thus apparently cut off from the scala vestibuli must form a spiral canal, included between the scala tympani on the one side and the scala vestibuli on the other; this canal is the *scala media* or *cochlear duct*.

The scala media is an endolymphatic canal. At the apex of the cochlea it ends in a blind extremity which is known as the *lagena* or *cecum cupulare*. Its opposite end forms a blind pouch between the fenestra cochleae and the fenestra vestibuli, at the base of the cochlea, which is termed the *cecum vestibulare*. The scala media is connected with the saccule and utricle by means of the canalis reuniens, as described above.

The scala tympani and scala vestibuli, on either side of the scala media, extend spirally from the base to the apex of the cochlea. At the apex they are united by the *helicotrema*, a continuation of these canals which curves around the hamulus. At the base of the cochlea the two canals diverge, the scala tympani ending abruptly at the fenestra cochleae, which is closed by a fibrous membrane, clothed on its tympanic surface by the flattened epithelium of the tympanic mucosa, and on its cochlear surface by the epithelium of the scala tympani. This *secondary tympanic membrane* serves for the relief of tension in the cochlea when the perilymph is set into motion by the stapes. The scala vestibuli, on the other hand, is continued backward into the vestibule, where it is in relation with the external surface of the saccule and utricle, and, since it is in contact with the outer wall of the bony vestibule, this portion of the scala vestibuli receives the opening of the fenestra vestibuli, which is closed by the foot plate of the stapes. Corresponding to the relative positions of the fenestra vestibuli and fenestra cochleae, the scala vestibuli in the first turn of the cochlea lies above the scala tympani, and being somewhat the longer it also extends farther backward.

Recent experimental evidence indicates that neither 'the oval nor the round

the pig, from whose cochlea he has been able to remove it entire. It is said to measure about 30 millimeters in length, to occupy the four turns of the cochlea, to be about five times as wide and five times as thick in the apical turn as at the basal end, and to have a section area in the apical turn approximately twenty-one times and a volume ninety-five times the area and volume of its basal end. It is described as consisting "of a hyaline matrix, probably keratin, in gelatinous form, in which are embedded the very numerous fine fibers or threads of uniform size." [9] The membrane has a slight amount of elasticity, is of a semisolid character and possesses marked adhesiveness; its specific gravity is said to be but little greater than that of the endolymph. None of the fibers extend the entire width of the membrane, none are attached at both ends, and the greater number are attached at neither end. [10] Hardesty describes a stripe (*Hensen's stripe*) on the under surface of the tectorial membrane opposite the row of inner hair cells, which he explains "as a line of intercrossing ends of fibers of the under surface resulting from the process by which the growth of the membrane terminates." He describes also a thin, exceedingly delicate, *accessory tectorial membrane*, along the under surface of the outer portion of the chief membrane. Only its outer edge is attached to the latter, and it is bounded internally by Hensen's stripe, thus covering only the outer hair cells.

Sulcus Spiralis Internus.—This is a deep groove included between the limbus spiralis and the axial attachment of the basilar membrane. It thus presents a vestibular lip and a tympanic lip. The basilar membrane is attached to the tympanic lip of the sulcus. The sulcus is lined by flattened epithelial cells, which are apparently continuous with those of the limbus, and like them are not readily distinguished from the underlying connective tissue. The epithelium is continued outward upon the basilar membrane to the margin of Corti's organ, with the innermost cells of which it is continuous.

Basilar Membrane (Membrana Basilaris).—This is a thin but resistant membranous structure, upon which rests the epithelium of Corti's organ. Hardesty describes it as a "flat tendon ... whose purpose is merely to strengthen the floor of the ductus cochlearis and the position of the organ of Corti, and the fibers of which are too rigid and firmly associated to allow of resonant vibration." Its tympanic surface is clothed by a continuation of the lining membrane of the scala tympani, consisting of a mesenchymal epithelium, resting upon a very thin and delicate connective tissue layer. The substantia propria of the basilar membrane consists of tendinous bands which, being radially disposed, span the interval between the margin of the tympanic lip of the internal sulcus and the opposed margin of the spiral ligament.

Because of the great breadth of the modiolus at the base, and its rapid diminution in thickness toward the apex of the cochlea, this interval is relatively narrow at the beginning of the first turn of the spiral scala media, but progressively widens as the apex of the cochlea is approached. Consequently, the shortest ten-

[9] Hardesty, 1914
[10] Hardesty, 1908.

which impinges upon the scala tympani slopes more abruptly. The greater portion of the spiral ligament, therefore, is contained within the scala media. Here it is covered by low columnar or cuboidal epithelium whose cells blend, without demarcation, with the underlying vascular connective tissue, so that the minute blood vessels frequently appear as if lying within the epithelial layer, although they probably are always contained within the connective tissue processes which project into the attached surface of the epithelial layer.

This very vascular subepithelial portion of the spiral ligament is known as the *stria vascularis*. A short distance above the point of attachment of the basilar membrane to the spiral ligament appears a prominent spiral ridge, the *prominentia spiralis*, the intervening groove constituting the *sulcus spiralis externus*. The larger blood vessel (venous) within the prominence is the *vas prominens*. From the external sulcus there extend into the subjacent ligamentous tissue numerous large clear clumps of epithelioid cells. These have been variously interpreted as neuro-epithelial elements and as smooth muscle cells. But Shambaugh [7] has shown that these groups of peculiar cells include tubules which open into the sulcus, and that they are in reality branched tubular glands. He ascribes to them the function of producing at least a portion of the endolymph of the scala media. The stria vascularis is probably also an important source of endolymph.

The tympanic wall or floor of the scala media presents for examination several structures, which, from within outward (*viz.*, from the modiolus to the ligamentum spirale), are the limbus spiralis, membrana tectoria, sulcus spiralis internus, basilar membrane, and the organ of Corti which rests upon the basilar membrane (Fig. 602).

Limbus Spiralis.—The limbus spiralis constitutes an elevation on the vestibular lip of the internal sulcus, which is formed by a peculiar cellular variety of connective tissue, *and is covered by columnar epithelium, whose cells are not sharply defined from those of the underlying connective tissue.* The surface of the epithelium presents a distinct cuticular formation of considerable thickness, which seems to be prolonged outward from the margin of the vestibular lip, and forms the membrana tectoria.

The surface of the limbus spiralis, when viewed from the scala media, presents slight elevations which, at the margin of the vestibular lip, are prolonged into prominent ridges whose indented borders overhang the sulcus and are known as the auditory teeth (of Huschke).

Membrana Tectoria (Membrane of Corti).—This is an exoplasmic or cuticular tissue, formed by the epithelium of the inner or limbus portion of the embryonic cochlear duct. It has a gelatinous fibrillar structure, but lacks nuclei. Unlike the otherwise very similar otolithic membranes of the maculae and cristae, it contains no calcareous products. Its free margin overhangs, or rests lightly upon, the hair cells of Corti's organ.

The tectorial membrane has been very carefully studied by Hardesty [8] in

[7] Shambaugh, 1908.
[8] Hardesty, 1908.
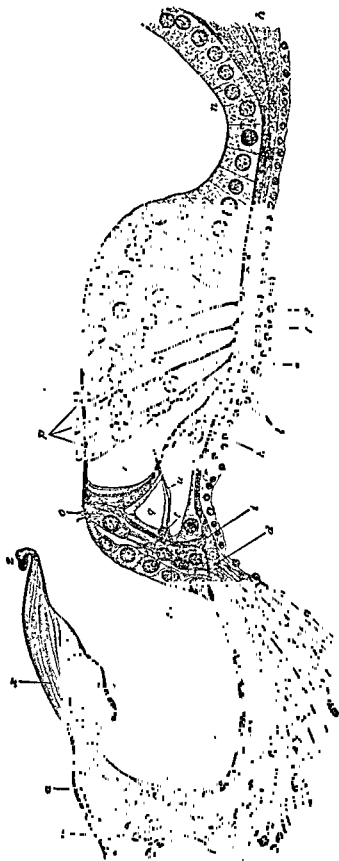
FIG. 602—A RADIAL SECTION THROUGH CORTI'S ORGAN IN THE FIRST TURN OF THE HUMAN COCHLEA.

a, vestibular lip of the lamina spiralis; *b*, sulcus spiralis internus; *c*, epithelium of the sulcus; *d*, nerve fibers penetrating a foramen nervosum; *e*, mesenchymal epithelium of the scala tympani; *f*, fibrous layer of the basilar membrane; *g*, cuticular layer; *h*, spiral ligament; *i*, inner, and *k*, outer pillars; *l*, Deiters' cells; *m*, Hensen's cells; *n*, cells of Claudius; *o*, inner, and *p*, outer hair cells; *q*, Corti's tunnel; *r*, Nuel's space; *s*, nerve plexus among the inner hair cells; *t*, plexus within the tunnel; *u*, tunnel fibers; *v*, plexus about the outer hair cells; *w*, *x*, *y*, *z*, membrana tectoria. ×405. (After Kölliker.)

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dinous fibers of the basilar membrane are found at the base of the cochlea, the longest at its apex. The shortest fibers are also the coarsest. It has been estimated that there are 24,000 distinct fibers or *auditory strings* in the basilar membrane. The shortest have a length of 0.041 millimeter, the longest 0.495 millimeter.

The substantia propria is covered upon that surface which faces the scala media by a thin homogeneous membrane, a cuticular formation or exoplasmic derivative, upon which rests the epithelium of the organ of Corti.

Organ of Corti.—This organ consists of a highly differentiated neuro-epithelium whose specialized cells are disposed according to a very regular arrangement. The flattened epithelium of the sulcus spiralis internus is continued for a short distance upon the basilar membrane. Suddenly, at the margin of Corti's organ, it alters its character. Here the epithelium becomes abruptly changed to a tall columnar variety, the first cells, known as the inner sustentacular cells, being apparently piled upon one another and resting against the inner hair cells, which form a single row of neuro-epithelium. These, like all the succeeding rows of cells, can be traced as a continuous line in the spirally wound scala media, from the base to the apex of the cochlea.

INNER AUDITORY OR HAIR CELLS.—The inner auditory or hair cells have a broad body which is confined to the superficial third of the epithelial layer and which is nucleated at its deeper end. Its free surface forms an expanded oval plate from which about twenty stiff cilia project through a cuticular membrane toward the cavity of the scala media. These end-plates interdigitate with the *phalanges* of the inner pillar cells, which are to be shortly described. The bases of the inner hair cells are thin and slender, and are in relation with a nerve plexus of fine fibrils derived from the terminal processes of the cochlear nerve. These nerve fibrils make their exit in small bundles from the bony spiral lamina, through the foramina nervosa and passing outward upon the basilar membrane are distributed in a plexus beneath the epithelium. Some of their naked processes almost immediately penetrate the epithelial layer to end between the bases of the inner hair cells.

The inner hair cells rest against the inner pillar cells, or rods, of *Corti's arch*. This arch is formed by two rows of highly specialized cells, the *inner* and the *outer pillars*, which are widely separated where their bases are attached to the basilar membrane, but are in contact at their free ends. The free extremity of the inner pillar is prolonged into a broad flattened plate-like process whose inner margin interdigitates with the head plate of the inner hair cells, as stated above, and whose outer margin is so prolonged as to almost, though not completely, cover the rounded head of the outer pillar. The head of the outer pillar, being similarly flattened, expanded, and prolonged outward beyond the margin of the head plate of the inner pillar cell, comes into contact with the phalanges of Deiters' cells and with the cilia of the outer hair cells which lie next without. A space is left between the outer pillars and the outer hair cells which is known as *Nuel's space*, filled with a semifluid intercellular substance.

The inner pillar cells are rather more numerous than the outer. In the entire

nucleated enlargement, beyond which they are continued only as an extremely slender basal process. The free ends of the outer hair cells present an expanded oval surface from which the hairs project. The outer hair cells are about five times as numerous as the inner, that is, there are about 3600 of the inner to 18,000 of the outer (Waldeyer). According to certain authorities the hair cells lack the delicate basal process in the adult condition.
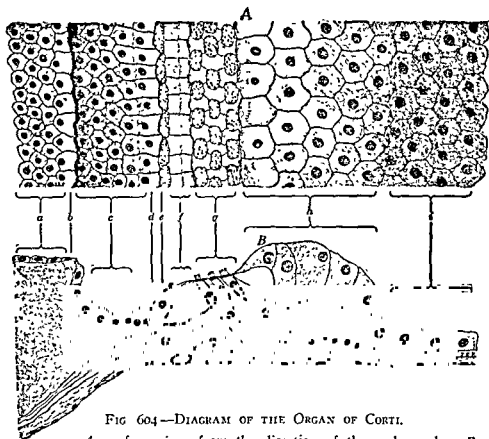
Fig 604—Diagram of the Organ of Corti.

A, surface view, from the direction of the scala media; B, as seen in section, profile view a, vestibular lip of the limbus spiralis; b, margin of same; c, sulcus spiralis internus; d, inner sustentacular cells; e, inner hair cells; f, pillar cells; g, outer hair cells and phalanges of Deiters' cells, h, cells of Hensen; i, cells of Claudius. Very highly magnified.

OUTER SUSTENTACULAR CELLS.—The outer sustentacular cells (Deiters' cells) are cylindrical cells whose expanded bases rest upon the basal membrane and whose distal portions extend toward the surface between the outer hair cells. The superficial portion of these cells, being encroached upon by the broad outer hair cells, is very slender; the broader basal portion occupies the deeper two-thirds of the neuro-epithelium, the spheroidal nuclei being found at the level of the middle third. Each sustentacular cell contains a *cuticular filament* (fiber of Retzius) which begins in contact with the cuticle of the basal membrane, and extends through the axis of the cell to its free border, where it expands to form a broad flattened plate of peculiar shape, known as the *phalangeal process*. These cuticular processes surround and overlie the margins of the head plates of the

length of the scala media, according to Retzius, there are 5600 inner pillars and 3850 outer pillars. Consequently about three of the expanded head plates of the inner pillars overlap two of the rounded heads of the outer pillar cells. The arch formed by the opposed pillar cells, being succeeded by similar arches of successive pillars, forms a continuous tunnel, triangular in transection, which extends the whole length of the scala media, and is known as the *canal of Corti*. This canal is also filled with a semifluid substance.

Each pillar cell is differentiated into two portions, the pillar proper and the basilar cell, the latter containing the nucleus. The pillar presents a fibrillar structure, the fibrils being disposed in the long axis of its body. This portion of the
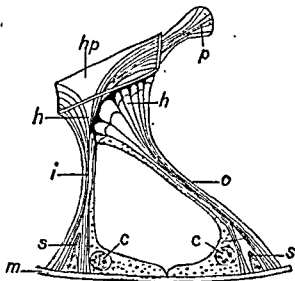
FIG. 603—SEMIDIAGRAMMATIC REPRESENTATION OF PILLARS OF CORTI.

i, inner pillar; *o*, outer pillar; *c*, inner and outer basal cells; *s*, supporting 'hillock' of inner and outer pillars; *m*, basilar membrane; *h*, head of inner and outer pillars; *p*, phalangeal plate of outer pillar, *hp*, head-plate of inner pillar. (Kolmer.)

cell reaches from the basilar membrane to the free surface of the neuro-epithelium.

The basal part of the cell, the basilar cell, probably represents the undifferentiated portion of the primordial pillar cell. It consists of a clear, finely granular cytoplasm and contains the spheroidal nucleus. It lies on that side of the pillar which faces the canal of Corti, the bases of the opposed cells being expanded until they meet, thus forming a cuticular floor for the tunnel. This undifferentiated basilar portion occupies only the deeper half of the pillar cell.

The rods of Corti are not present in the cochlea of birds. They are apparently not an essential part of the auditory mechanism. They presumably assist in rendering the organ of Corti more sensitive as an apparatus for tone perception.

OUTER HAIR CELLS.—The outer hair cells form three to five rows of ciliated cells which are similar in structure to the inner hair cells, and which are supported by the sustentacular cells of Deiters. Their cylindrical cell bodies occupy the superficial third of the epithelial layer and at the deeper extremity present a

Acoustic Nerve.—The acoustic nerve presents two distinct divisions both of which are sensory, but which differ greatly as regards their central termination. They likewise differ in their peripheral distribution. Within the internal acoustic meatus the nerve divides, each branch consisting of numerous bundles. The vestibular (superior or anterior) division is supplied with a ganglion of considerable size, the *vestibular ganglion (of Scarpa)*, beyond which the nerve separates into three branches which supply, respectively, the macula of the utricle, and the cristae of the superior and lateral semicircular ducts, in the neuro-epithelium of each of which their terminal fibrils end in relation with the bases of the hair cells (Figs.

FIG 605—AXIAL SECTION THROUGH CORTI'S ORGAN OF THE GUINEA-PIG, SHOWING THE TERMINAL NERVE FIBRILS.

B, cells of Böttcher; *D¹*, *D²*, *D³*, three rows of Deiters' cells; *H*, cells of Hensen; *i.b.*, inner border cell; *i h*, inner hair cell; *i p*, inner pillar cell; *n*, terminal branch of the cochlear nerve; *o h.*—*1*, *2*, *3*, three rows of outer hair cells; *o p*, outer pillar cell; *p*, phalangeal process of the outer sustentacular process. Very highly magnified (Held.)

597, 598). The remaining nerve fibers which are distributed to the vestibule are said to be derived from a branch of the cochlear (inferior or posterior) division, and to supply in a similar manner the macula of the saccule and the crista of the posterior semicircular duct. According to Streeter,[12] the vestibular nerve contributes also the innervation to the posterior duct and to the saccule, the cochlear nerve supplying only the cochlea.

The cochlear branch proper, cochlear nerve, enters the modiolus, where it becomes abruptly narrowed by giving off numerous fine branches which pass outward between the layers of the bony spiral lamina. Here they form a continuous spiral succession of small nerve trunks, supplied with many bipolar ganglion cells, which collectively form the *spiral ganglion* (Fig. 601). They penetrate the margin of the bony sulcus through the *foramina nervosa*, a succession of perforations, in the tympanic lip of sulcus. Here the nerve fibers lose their myelin sheath and come almost at once into relation with the inner hair cells. From this

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[12] Streeter, 1907.

hair cells, thus forming a reticular layer through the openings of which the cilia of the hair cells project.

The cells of Deiters are succeeded by the sustentacular *cells of Hensen*. These are tall columnar cells. There are about eight rows of these cells, the innermost of which equal in height the tall cells of the preceding type. The cells of the outer rows become abruptly shortened. Here they pass into the cuboidal *cells of Claudius*, and are thus continued outward to the spiral ligament.

The nuclei of the cells of Hensen are found in their superficial third, those of the cells of Claudius in the center of the cell. Beneath Hensen's cells other small nucleated elements are occasionally found. They give to this layer somewhat the appearance of a two-rowed epithelium and are known as the *cells of Böttcher*.

Both the cells of Hensen and those of Claudius are provided with a cuticular margin which, with the similar cuticle of the cells of Deiters, forms a continuous, membranous, cuticular layer known as the *lamina reticularis*. The inner portion of this cuticular membrane is pierced by the cilia of the three to five rows of outer hair cells, as already described.

A fibrillar axial core is a common feature of all of the sustentacular elements of Corti's organ. This *fiber of Retzius* becomes progressively less pronounced in passing from the pillar cells, where it is very highly developed, to the cells of Claudius, where it is barely discernible.

In the above description we have directed attention to the appearance of transections of the organ of Corti. In the study of this organ in the fresh condition, and occasionally in fixed and stained preparations, it is possible to obtain a surface view of this organ from the direction of the scala media. In such preparations the polygonal outlines of the columnar cells of the limbus spiralis, beneath which are the auditory teeth, are seen on the outer side of the attachment of Reissner's membrane. Beneath the overhanging edge of the limbus the mosaic of large polygonal epithelial cells of the internal sulcus comes into view. At the margin of the organ of Corti these are exchanged for the broader ends of the inner sustentacular cells and the adjacent single row of inner hair cells.

The flattened rectangular head plates of the inner pillar cells form the next row, the heads of the outer pillars projecting from beneath, and extending beyond the heads of the inner pillar cells. These are followed by the interdigitating phalanges of the cells of Deiters, which enter into the formation of the reticular membrane, through the fenestra of which the cilia of the three to five rows of outer hair cells project. This cuticular membrane is continued outward, and beneath it are successively seen the ends of the cells of Hensen, and of the cells of Claudius.

The average total length of the organ of Corti in sixty-eight cochleae from individuals ten weeks to eighty-five years of age, as determined by Hardy,[11] is 31.52 mm, the range being from 25 26 to 35 45 mm. The number of turns is from two and one-half to two and three-fourths in 87 per cent of these cases, nine of these cochleae having exactly two and one-half turns. Eight cochleae have more than two and three-fourths but less than three turns. She interprets her data as indicating a slight increase in length with age, without an increase in the number of turns. The organ of Corti is said to be on the average slightly longer in the right than in the left cochlea, and slightly longer in males than in females. The data indicate no racial difference.

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11 Hardy, 1938.

Acoustic Nerve.—The acoustic nerve presents two distinct divisions both of which are sensory, but which differ greatly as regards their central termination. They likewise differ in their peripheral distribution. Within the internal acoustic meatus the nerve divides, each branch consisting of numerous bundles. The vestibular (superior or anterior) division is supplied with a ganglion of considerable size, the *vestibular ganglion (of Scarpa)*, beyond which the nerve separates into three branches which supply, respectively, the macula of the utricle, and the cristae of the superior and lateral semicircular ducts, in the neuro-epithelium of each of which their terminal fibrils end in relation with the bases of the hair cells (Figs.

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B, cells of Böttcher; D^1, D^2, D^3, three rows of Deiters' cells; *H*, cells of Hensen; *i.b.*, inner border cell; *i.h.*, inner hair cell; *1 p.*, inner pillar cell; *n*, terminal branch of the cochlear nerve; *o h.—1, 2, 3*, three rows of outer hair cells; *o p.*, outer pillar cell; *p*, phalangeal process of the outer sustentacular process. Very highly magnified. (Held)

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The cochlear branch proper, cochlear nerve, enters the modiolus, where it becomes abruptly narrowed by giving off numerous fine branches which pass outward between the layers of the bony spiral lamina Here they form a continuous spiral succession of small nerve trunks, supplied with many bipolar ganglion cells, which collectively form the *spiral ganglion* (Fig. 601). They penetrate the margin of the bony sulcus through the *foramina nervosa*, a succession of perforations, in the tympanic lip of sulcus. Here the nerve fibers lose their myelin sheath and come almost at once into relation with the inner hair cells. From this

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[12] Streeter, 1907.

hair cells, thus forming a reticular layer through the openings of which the cilia of the hair cells project.

The cells of Deiters are succeeded by the sustentacular *cells of Hensen*. These are tall columnar cells. There are about eight rows of these cells, the innermost of which equal in height the tall cells of the preceding type. The cells of the outer rows become abruptly shortened. Here they pass into the cuboidal *cells of Claudius*, and are thus continued outward to the spiral ligament.

The nuclei of the cells of Hensen are found in their superficial third, those of the cells of Claudius in the center of the cell. Beneath Hensen's cells other small nucleated elements are occasionally found. They give to this layer somewhat the appearance of a two-rowed epithelium and are known as the *cells of Böttcher*.

Both the cells of Hensen and those of Claudius are provided with a cuticular margin which, with the similar cuticle of the cells of Deiters, forms a continuous, membranous, cuticular layer known as the *lamina reticularis*. The inner portion of this cuticular membrane is pierced by the cilia of the three to five rows of outer hair cells, as already described.

A fibrillar axial core is a common feature of all of the sustentacular elements of Corti's organ. This *fiber of Retzius* becomes progressively less pronounced in passing from the pillar cells, where it is very highly developed, to the cells of Claudius, where it is barely discernible.

In the above description we have directed attention to the appearance of transections of the organ of Corti. In the study of this organ in the fresh condition, and occasionally in fixed and stained preparations, it is possible to obtain a surface view of this organ from the direction of the scala media. In such preparations the polygonal outlines of the columnar cells of the limbus spiralis, beneath which are the auditory teeth, are seen on the outer side of the attachment of Reissner's membrane. Beneath the overhanging edge of the limbus the mosaic of large polygonal epithelial cells of the internal sulcus comes into view. At the margin of the organ of Corti these are exchanged for the broader ends of the inner sustentacular cells and the adjacent single row of inner hair cells.

The flattened rectangular head plates of the inner pillar cells form the next row, the heads of the outer pillars projecting from beneath, and extending beyond the heads of the inner pillar cells. These are followed by the interdigitating phalanges of the cells of Deiters, which enter into the formation of the reticular membrane, through the fenestra of which the cilia of the three to five rows of outer hair cells project. This cuticular membrane is continued outward, and beneath it are successively seen the ends of the cells of Hensen, and of the cells of Claudius.

The average total length of the organ of Corti in sixty-eight cochleae from individuals ten weeks to eighty-five years of age, as determined by Hardy,[11] is 31.52 mm, the range being from 25.26 to 35.45 mm. The number of turns is from two and one-half to two and three-fourths in 87 per cent of these cases, nine of these cochleae having exactly two and one-half turns. Eight cochleae have more than two and three-fourths but less than three turns. She interprets her data as indicating a slight increase in length with age, without an increase in the number of turns. The organ of Corti is said to be on the average slightly longer in the right than in the left cochlea, and slightly longer in males than in females. The data indicate no racial difference.

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[11] Hardy, 1938

Acoustic Nerve.—The acoustic nerve presents two distinct divisions both of which are sensory, but which differ greatly as regards their central termination. They likewise differ in their peripheral distribution. Within the internal acoustic meatus the nerve divides, each branch consisting of numerous bundles. The vestibular (superior or anterior) division is supplied with a ganglion of considerable size, the *vestibular ganglion (of Scarpa)*, beyond which the nerve separates into three branches which supply, respectively, the macula of the utricle, and the cristae of the superior and lateral semicircular ducts, in the neuro-epithelium of each of which their terminal fibrils end in relation with the bases of the hair cells (Figs.

FIG. 605—AXIAL SECTION THROUGH CORTI'S ORGAN OF THE GUINEA-PIG, SHOWING THE TERMINAL NERVE FIBRILS.

B, cells of Böttcher; *D¹, D², D³,* three rows of Deiters' cells; *H,* cells of Hensen; *i b.,* inner border cell; *i.h.,* inner hair cell; *i.p.,* inner pillar cell; *n,* terminal branch of the cochlear nerve; *o h.—1, 2, 3,* three rows of outer hair cells; *o p,* outer pillar cell; *p.,* phalangeal process of the outer sustentacular process. Very highly magnified. (Held.)

597, 598). The remaining nerve fibers which are distributed to the vestibule are said to be derived from a branch of the cochlear (inferior or posterior) division, and to supply in a similar manner the macula of the saccule and the crista of the posterior semicircular duct. According to Streeter,[12] the vestibular nerve contributes also the innervation to the posterior duct and to the saccule, the cochlear nerve supplying only the cochlea.

The cochlear branch proper, cochlear nerve, enters the modiolus, where it becomes abruptly narrowed by giving off numerous fine branches which pass outward between the layers of the bony spiral lamina. Here they form a continuous spiral succession of small nerve trunks, supplied with many bipolar ganglion cells, which collectively form the *spiral ganglion* (Fig. 601). They penetrate the margin of the bony sulcus through the *foramina nervosa*, a succession of perforations, in the tympanic lip of sulcus. Here the nerve fibers lose their myelin sheath and come almost at once into relation with the inner hair cells. From this

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[12] Streeter, 1907.

point the path of the unmyelinated fibers varies, most of them passing for some distance along a spiral course through the organ of Corti. One such spiral bundle is found on the inner, and another on the outer side of the inner pillars, the latter lying within the canal of Corti. Still other fibers, the *tunnel fibers*, cross the canal of Corti to form a spiral plexus beneath the outer hair cells and the cells of Deiters.

FIG 606.—SCHEME OF THE VASCULAR SUPPLY OF THE INTERNAL EAR.

C^1, first turn of the cochlea; *S*, saccule; *Sup.S.C.*, *Ext.S.C.*, and *Post S.C.*, superior, external, and posterior semicircular canals; *U*, utricle. The arteries are in heavy black, the veins somewhat lighter; *a*, central vein, and *b*, central artery of the cochlea; *c*, vestibular artery; *d*, vestibulocochlear artery; *e*, *arteria propria cochleae*; *f*, vena aqueductus cochlea; *g*, vena aqueductus vestibuli.

Terminal fibrils from these spiral plexuses end in relation with both the inner and the outer hair cells.

The relation of the *nerve cells of the spiral ganglion* and the *vestibular ganglion* to the termination of the nerve fibrils about the hair cells of the organ of Corti, the maculae, and the cristae, is essentially the same. The ganglia contain the cell bodies of the peripheral sensory neurons of the eighth cerebral or acoustic nerve. These are bipolar cells, of which the central *process* or axon enters a myelinated nerve fiber of the acoustic nerve, while the peripheral process is distributed to the hair cells of the several areas of specialized neuro-epithelium, as above described.

Vascular Supply.—*Blood Supply.*—The internal ear is supplied by the *internal auditory artery*, a branch of the basilar artery, which enters the labyrinth along with the acoustic nerve, and at once divides into two main stems, the vestibular and the cochlear (arteria cochlearis communis, Siebenmann). The *vestibular artery*

accompanies the branches of the vestibular nerve to the saccule, utricle, and semicircular ducts, supplying these structures in the posterior portion of the vestibule, and forming a rich plexus in the connective tissue of the maculae and cristae, and a more scanty network in the remaining portions of the membranous labyrinth.

The cochlear division of the internal auditory artery, according to Siebenmann, promptly subdivides into the *cochlear artery* proper, which appears as the continuation of the vessel, and the *vestibulocochlear artery,* which supplies the macula sacculi, the posterior ampulla, and the adjacent portions of the utricle and posterior
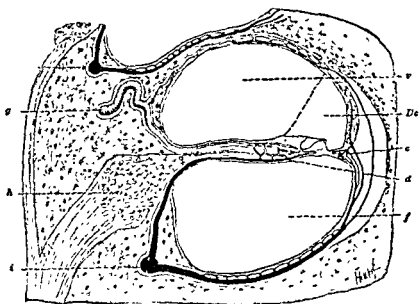
FIG 607.—SCHEME OF THE VASCULAR TERMINATIONS IN THE WALL OF THE COCHLEAR CANALS.

c, capillary vessels in the spiral ligament; *Dc,* cochlear duct or scala media, *d,* capillaries in the limbus spiralis; *f,* scala tympani, *g,* arteriole; *h,* spiral ganglion; *i,* vena spiralis inferior, *v,* scala vestibuli; *j,* vena spiralis superior (Böhm and von Davidoff.)

semicircular duct. This vessel also supplies the early portion of the first turn of the spiral cochlea.

The true cochlear artery enters the modiolus and supplies a branch to the remaining portion of the first cochlear turn, and a terminal branch which passes as far as the apex of the cochlea, distributing its branches to the last two turns. All of these vessels are characterized by their peculiarly tortuous course. They distribute terminal branches to the limbus spiralis and to the connective tissue of the membranous scala vestibuli, extending as far around this canal as the spiral ligament. No vessels cross in the basilar membrane.

The veins collect the blood from the limbus spiralis and the wall of the scala tympani and form venous trunks within the modiolus, which correspond more or less closely with the arteries. Two of the cochlear radicles of the venous tributaries are important by reason of their position and relative size: the *vas prominens* of the prominentia spiralis of the stria vascularis, and the *vas spiralis* beneath the organ of Corti. Those veins coming from the wall of the scala tympani unite to form superior and inferior spiral veins in the inner wall of the scala tympani.

point the path of the unmyelinated fibers varies, most of them passing for some distance along a spiral course through the organ of Corti. One such spiral bundle is found on the inner, and another on the outer side of the inner pillars, the latter lying within the canal of Corti. Still other fibers, the *tunnel fibers*, cross the canal of Corti to form a spiral plexus beneath the outer hair cells and the cells of Deiters.

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theory, a modification of the earlier telephone theory of Rutherford (1886); and he has succeeded in constructing an apparatus which simulates the cochlea, and imitates its presumed functional activity at least in the lower ranges of the tone scale.

Hardesty [15] suggests "that notes up to a certain pitch throw the entire natural tectorial membrane into vibrations of corresponding frequencies and that sensations of pitch are determined by the frequency of impingement of the membrane upon the auditory hairs, intensity being determined by the amplitude and quality by the quality of the wave motion imparted. Further, that the highest notes within the range of the auditory apparatus throw, according to their frequency, only varying extents of the smaller, basal end of the tectorial membrane into vibration, being so damped out in passing toward the apex of the cochlea, overcoming friction, the inertia of the endolymph and that of the membrane itself, as not to produce vibrations in the heavier, apical portions"

In essence, the tectorial membrane is conceived to respond in its several parts in the manner of a physical resonator to tones of different pitch (Shambaugh). According to this conception, tone analysis is accomplished peripherally, the specific stimulus being carried to the brain by the special sets of cochlear nerve fibers.

DEVELOPMENT OF THE EAR

The external ear develops in connection with the first branchial furrow: the meatus from the deepened groove, the auricle through the fusion of definite tubercles on the adjacent branchial arches.

The middle ear and auditory tube arise from the corresponding pharyngeal pouch, the process involving a ventral elongation of the groove to form the tube and a subse-

FIG. 608.—SEMIDIAGRAMMATIC ILLUSTRATIONS OF SUCCESSIVE STAGES IN THE DEVELOPMENT OF THE INTERNAL EAR OF THE CHICK.

A, forty-five-hour embryo; *B*, sixty-hour embryo; *C*, five-day embryo; *D*, seven-day embryo; *M*, wall of neural canal at level of metencephalon; *E*, epidermal ectoderm; *op*, otic pit, *oc*, otocyst (otic vesicle); *DE*, ductus endolymphaticus; *SE*, saccus endolymphaticus; *cd*, cochlear duct; *u*, utriculus; *dss*, superior semicircular duct; *dsl*, lateral semicircular duct.

quent dorsal dilatation, expanding as the tympanum to include the auditory ossicles which have meanwhile taken form in the adjacent mesenchyma. The mastoid cells are formed by a late erosion and invasion of the bone by the mucous membrane of the tympanum.

The internal ear develops from a thickening in the epidermal *ectoderm* at the level

[15] Hardesty, 1914.

These vessels chiefly empty into the *vena aqueductus cochleae* which finds its way through the aqueduct to the internal jugular vein. Other branches from the interior of the cochlea unite to form the central vein of the cochlea, which becomes the chief radicle of the *internal auditory vein*, and thus enters either the transverse or inferior petrosal sinus.

The veins from the utricle and semicircular canals mostly enter the *vena aqueductus vestibuli* (aqueduct of Cotunnius), which follows its aqueduct to the superior petrosal sinus.

It will be perceived that the blood has three chief avenues of exit from the labyrinth: by the vena aqueductus vestibuli, by the *vena aqueductus cochleae* and by the internal auditory vein. The greater portion of the blood pursues the second course and thus finds its way to the internal jugular vein, the smaller remainder entering the petrosal sinuses by one of the other two avenues.

Lymphatics.—The internal ear contains relatively few lymphatic vessels but is richly supplied with broad lymphatic spaces. Anastomosing vessels are found in the periosteum and membranous wall of the labyrinth. These communicate with the perilymph spaces between the periosteum and the membranous wall in the vestibule, and with the vestibular and tympanic scalae in the cochlea. The perilymphatic spaces are connected with the subdural space of the meninges by means of lymphatic channels in the aqueductus cochleae. The perilymph of the vestibule also communicates with the subdural space through vessels which follow the sheaths of the nerves.

The endolymph cavities of the several divisions of the membranous labyrinth communicate freely with one another. By means of the ductus endolymphaticus a connection is also established through the aqueductus vestibuli with the subdural space, the blind terminal saccule of this canal, the *saccus endolymphaticus* lying upon the posterior surface of the petrous bone and in contact with the dura mater.

FUNCTION OF THE COCHLEA

The cochlea is the essential organ of hearing. The fundamental structure concerned in audition is the spiral organ of Corti. The physiology of sound perception involves proximally the stimulation of the hair cells of Corti's organ by the tectorial membrane. This membrane is thrown into synchronous vibrations by the undulations in the endolymph of the cochlear duct transmitted through the vestibular membrane from the perilymph. The latter receives the sound waves through the foot plate of the stapes.

The Helmholtz (1896) theory of tone perception, formerly widely accepted, postulated sympathetic vibrations, in resonance with atmospheric waves, on the part of the fibers of the basilar membrane. This view has been shown to be untenable, notably by Shambaugh [13] and by Hardesty.[14] The basilar membrane contains only a little more than half as many fibers as the maximum number of vibrations (40,000 double vibrations per second) commonly audible; moreover, it does not possess the physical and histologic properties demanded by the resonance theory of tone perception. Hardesty has shown that the tectorial membrane on the contrary does answer the requirements of an alternative

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13 Shambaugh, 1908.
14 Hardesty, 1908.

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13 Shambaugh, 1908
14 Hardesty, 1908.

one between the saccule and the oval window, the other between the saccule and the round window. From these two areas the two great scalae of the cochlea proceed in a definite and constant direction to their definitive position and condition.[16]

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[16] Streeter, 1916.

of the third primary cerebral vesicle. This auditory primordium becomes invaginated to form an *otic pit*, the aperture of which subsequently closes and thus separates an *auditory vesicle* or *otocyst* from the overlying parent ectoderm. At the point of closure medially a dorsal evagination arises to form the endolymphatic duct. At the upper pole of the vesicle appear the *semicircular ducts* through a process involving the elevation of three circular folds, the lateral walls of which fuse proximally, and subsequently disappear leaving a peripheral duct dilated at one end to form an *ampulla*. The cochlea arises at the opposite pole as a tubular evagination which becomes spirally disposed. The original vesicle persists as the *utricle*. On its anteromedial border is formed an
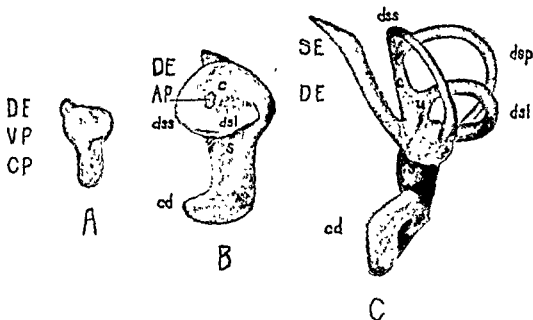
FIG. 609.—WAX RECONSTRUCTIONS OF THREE EARLY STAGES, IN THE DEVELOPMENT OF THE INTERNAL EAR (MEMBRANOUS LABYRINTH) OF MAN.

A, lateral view, from a 6.6 millimeter embryo; *B*, lateral view from an 11 millimeter embryo; *C*, front view from a 20 millimeter embryo (*A* and *B* correspond approximately to stages *C* and *D* of the preceding figure). *DE*, ductus endolymphaticus; *SE*, saccus endolymphaticus; *VP*, vestibular pouch; *cp*, cochlear pouch; *ap*, absorption focus; *c*, crus; *s*, sacculus; *u*, utriculus; *cd*, cochlear duct; *dss, dsp,* and *dsl,* superior, posterior, and lateral semicircular ducts. (After Streeter.)

alveolar evagination, the *saccule*, which remains connected by a constricted duct, the *utriculosaccular canal*, to which is attached the ductus endolymphaticus.

Each ampulla differentiates an elongated patch of neuro-epithelium, the *cristae*. In both utricle and saccule a similar oval patch appears, the *maculae*. The *spiral organ* of the cochlea develops in like manner through a specialization of the ectoderm along the floor of the membranous duct.

The *bony labyrinth* develops from the mesenchyma originally enveloping the membranous labyrinth. The mesenchyma immediately surrounding the membranous labyrinth becomes converted into a mucoid tissue which eventually disappears, leaving the perilymphatic spaces. These spaces are bounded by periosteum, the innermost layer of which becomes modified into a mesenchymal epithelium.

The *scala tympani* and *scala vestibuli* of the cochlea are formed by the coalescence and subsequent dilatation of small mesenchymal tissue spaces in two distinct regions:

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